DESIGN, DEVELOPMENT AND OPTIMIZATION OF CONTROLLED RELEASE TABLET OF FLUCONAZOLE

Dissertation submitted to

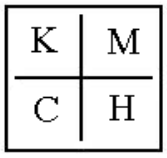
The Tamilnadu Dr. M.G.R Medical University, Chennai

In partial fulfillment for the requirement of the degree of

MASTER OF PHARMACY

(Pharmaceutics)

SEPTEMBER-2012



DEPARTMENT OF PHARMACEUTICS

KMCH COLLEGE OF PHARMACY

KOVAI ESTATE, KALAPPATTI ROAD, COIMBATORE-641048

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Submitted by

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Reg.No:**26107117**

Under the Guidance of

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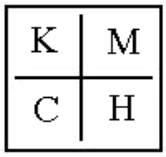

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Professor of Pharmaceutics.

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN, DEVELOPMENT AND OPTIMIZATION OF CONTROLLED RELEASE TABLET OF FLUCONAZOLE"** Submitted by **SUBBA RAGHAVENDRA RAO.M,** Reg. No: **26107117** to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by the candidate at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, and was evaluated by us during the academic year 2011 – 2012.

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DECLARATION

I do hereby declare that this dissertation entitled **"DESIGN, DEVELOPMENT AND OPTIMIZATION OF CONTROLLED RELEASE TABLET OF FLUCONAZOLE"** submitted to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of Master of Pharmacy in Pharmaceutics was done by me under the guidance of **Prof. Dr. C.SANKAR, M.Pharm., Ph.D.,** Professor, Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the year 2011 – 2012.

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ABBREVIATIONS USED

e.g.	Example
i.e.	That is
%	Percentage
Kg	Kilogram
gm	gram
mg	Milligram
µg	Microgram
ml	Millilitre
cm	Centimetre
mm	millimetre
nm	nanometre
W/w	Weight by weight
V/v	Volume by volume
avg	Average
hrs	Hours
pH	Hydrogen ion concentration
°C	Degree centigrade
HCL	Hydrochloric acid
RPM	Revolution per minute
Abs	Absorbance
Conc.	Concentration
Fig	Figure

UV- VIS	Ultra violet and visible spectroscopy
FTIR	Fourier Transform Infra Red spectroscopy
C.I	Compressibility Index
CR	Cumulative Release
AMS	Anti microbial study
ZOI	zone of inhibition
SS	sum of squares
df	degrees of freedom
MS	mean square
Sig	significance

ABSTRACT

The purpose of this research was to prepare controlled release tablets of Fluconazole in reducing the dose and increasing efficiency with reducing fluctuations.By controlling the rate of release the side effects such as hallucinations and paranoid behaviour will also be minimized.A 2^2 factorial design was employed to optimize the formulations,producing 4 factorial points,this design generally involves dependent variables Y,independent variable X.The independent variable selected for this study were (X1-X4),X1amount of maltodextrin,X2 amount of Carbopol 940, X3 amount of HPMC,X4 amount of Ethyl cellulose.The dependent variable were (Y1-Y4),Y1 hardness,Y2 amount of drug release at 1st hour, Y3 time taken to reach t50%, Y4 Zone of inhibition.Controlled release release tablets have been prepared incorporating antifungal drug Fluconazole using polymers like Maltodextrin,HPMC,Carbopol 940,Ethyl Cellulose.The anti microbial studies showed good antifungal activity based on zone of inhibition.The invitro drug release studies revealed that as the concentration of polymer increased the drug release decreased.Formulations containing higher concentration of polymers were able to efficiently control Fluconazole release over a time period of 8hrs.The formulations containing 2:2 ratio of polymers gave the best results, among which the formulation containing Carbopol-940:HPMC with 2:2 ratio of polymers is concluded as best formulation in terms of required drug release in a controlled release manner. The drug release mechanism was confirmed as case-II transport or typical zero-order release.IR spectra matching confirmed that there was no major interaction between the drug and the excipients used.

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INTRODUCTION

CONTROLED RELEASE DRUG ADMINISTRATION:

During the last two decades there has been remarkable increase in interest in controlled release drug delivery system[1]. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of controlled release is also being applied to veterinary products.

Modified Release Dosage Forms[2]: According to the United States Pharmacopoeia the term 'modified release dosage forms' is used to denote the dosage forms for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic objectives not offered by the conventional dosage forms. Two types of modified release dosage forms are recognised.

1] Extended release dosage forms:

It is defined as the one that allows at least a two fold reduction in the dosing frequency as compared to that of conventional dosage form.

2] Delayed release dosage forms:

It is defined as one that releases the drug at a time other than "immediately" after administration.

Rationale of controlled drug delivery[3]

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration.

Different terminologies have been used for the new drug delivery system by different authors.

A] Controlled Action:

In this type of dosage forms it provides a prolonged duration of drug release with predictability and reproducibility of drug release kinetics. In this case, the rate of drug absorption is equal to the rate of drug removal from body.

2] Sustained Action:

In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose.

3] Prolonged Action:

These types of dosage form are designed in such a way that it release the drug over an extended period during which pharmacological response is obtained but does not necessarily maintain the constant blood level.

4] Site specific and receptor release:

It refers to targeting of drug directly to a certain biological location.

Potential advantages and disadvantages of controlled release dosage forms :

Advantages [4-7]:

i] Patient Compliance:

Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule. Also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and or systemic side effect of the dosage form.

The problem of lack of patient compliance can be resolved to some extent by administering controlled release drug delivery system.

ii] Reduced 'see- saw' fluctuation:

Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see – saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well designed controlled release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a more steady drug concentration in blood

circulation and target tissue cells.

iii] Reduced total dose:

Controlled release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

iv] Improved efficiency in treatment:

Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A controlled release dosage forms leads to better management of the acute or chronic disease condition.

Disadvantages[5-7] :

i) Dose dumping:

Dose dumping is a phenomenon where by relatively large quantities of drug in a controlled release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index.

e.g: Phenobarbital.

ii) Less flexibility in accurate dose adjustment:

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

iii) Poor *In vitro – In vivo* correlation:

In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called

'Absorption window' becomes important and may give rise to unsatisfactory drug absorption *in vivo* despite excellent in-vitro release characteristics.

iv) Patient variation:

The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

Fig.1: Controlled release drug delivery system

Criteria to be met by drug proposed to be formulated in controlled release dosage forms[5,6]:

a) Desirable half-life.

b) High therapeutic index

c) Small dose

d) Desirable absorption and solubility characteristics.

e) Desirable absorption window.

f) First past clearance.

DESIGN AND FORMULATION OF ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM AND THE FACTORS AFFECTING THEREOF[7-10]:

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu.

- Theoretically and desirably a controlled release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion.
- Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order controlled release formulation.
- Controlled (zero-order) drug release has been attempted to be achieved, by following classes of controlled drug delivery system[8].

A)Diffusioncontrolledsyste m

i) Reservoir type.

ii) Matrix type

B) Dissolution controlled system.

i) Reservoir type.

ii) Matrix type

C) Methods using Ion-exchange.

D) Methods using osmotic pressure.

E) pH independent formulations.

F) Altered density formulations

Drug properties influencing the design of sustained or controlled release drug delivery system are classified as :

1] Physicochemical properties of the drug

These include dose size, aqueous solubility, protein binding, molecular size, drug stability and partition coefficients.

2] Biological factors

These include absorption, distribution, metabolism, duration of action, margin of safety, side effects of drug, disease state and circadian rhythm.

Methods to achieve oral controlled drug delivery[8]:

There are various methods employed for the fabrication of oral controlled release delivery systems. Ritschel has given a detailed report of these techniques. These are as follows.

a. Hydrophilic matrix

b. Plastic matrix

c. Barrier resin beads

d. Fat embedment

e. Repeat action

f. Ion exchange resin

g. Soft gelatin depot capsules

h. Drug complexes

Evaluation of controlled release Tablets:

Before marketing a controlled release product, it is must to assure the strength, safety,

stability and reliability of a product by forming in-vitro and in-vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for controlled release formulations.

1. In – Vitro Methods

These are:-

a. Beaker method

b. Rotating disc method

c. Rotating Bottle method d.

d .Rotating Basket method

e. Stationary Basket Method

f. Oscillating tube method

g. Dialysis method

h. USP dissolution method.

2. In–Vivo Methods

Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are:-

a. Clinical response

b. Blood level data

c. Urinary excretion studies

d. Nutritional studies.

e. Toxicity studies

f. Radioactive tracer techniques

FACTORIAL DESIGN[11-14] :

Factorial design is an important method to determine the effects of multiple variables on a response. Traditionally, experiments are designed to determine the effect of ONE variable upon ONE response. R.A. Fisher showed that there are advantages by combining the study of multiple variables in the same factorial experiment. Factorial design can reduce the number of experiments one has to perform by studying multiple factors simultaneously. Additionally, it can be used to find both main effects (from each independent factor) and interaction effects (when both factors must be used to explain the outcome). However, factorial design can only give relative values, and to achieve actual numerical values the math becomes difficult, as regressions (which require minimizing a sum of values) need to be performed. Regardless, factorial design is a useful method to design experiments in both laboratory and industrial settings.

- Factorial design tests all possible conditions. Because factorial design can lead to a large number of trials, which can become expensive and time-consuming, factorial design is best used for a small number of variables with few states (1 to 3). Factorial design works well when interactions between variables are strong and important and where every variable contributes significantly.
- Factorial Designs are used in experiments where the effects of different factors, or conditions, on experimental results are to be elucidated.some practical examples where factorial designs are optimal are experiments to determine the effect of pressure and lubricant on the hardness of a tablet formulation, to determine the efect of disintegrant and lubricant concentration on tablet dissolution, or to determine the efficacy of a combination of two active ingredients in an over-the-counter cough preparation.
- Factorial designs are the designs of choice for simultaneous determination of the effects of several factors and their interactions.

Introduction to Design of Experiments (DOE) - DOE Types

The design and analysis of experiments revolves around the understanding of the effects of different variables on other variable(s).

- In mathematical jargon, the objective is to establish a *cause-and-effect* relationship between a number of *independent variables* and a *dependent variable* of interest. The dependent variable, in the context of DOE, is called the *response*, and the independent variables are called *factors*.
- Experiments are run at different factor values, called *levels*. Each run of an experiment involves a combination of the levels of the investigated factors. Each of the combinations is referred to as a *treatment*. In a single factor experiment, each level of the factor is referred to as a treatment.
- In experiments with many factors, each combination of the levels of the factors is referred to as a treatment. When the same number of response observations are taken for each of the treatments of an experiment, the design of the experiment is said to be *balanced*. Repeated observations at a given treatment are called *replicates*. The number of treatments of an experiment is determined on the basis of the number of factor levels being investigated in the experiment.
- For example, if an experiment involving two factors is to be performed, with the first factor having x levels and the second factor having z levels, then x z treatment combinations can possibly be run, and the experiment is an x z factorial design.

- If all x z combinations are run, then the experiment is a full factorial. If only some of the xz treatment combinations are run, then the experiment is a fractional factorial.

In full factorial experiments, all of the factors and their interactions are investigated, whereas in fractional factorial experiments, all interactions are not considered because not all treatment combinations are run.

- It can be seen that the size of an experiment escalates rapidly as the number of factors, or the number of the levels of the factors, increases. For example, if two factors at three levels each are to be used, nine different treatments are required for a full factorial experiment (3 3 = 9). If a third factor with three levels is added, 27 treatments are required (333 = 27) and 81 treatments are required if a fourth factor with three levels is added (3333 = 81). If only two levels are used for each factor, then in the four factor case, 16 treatments are required (2 2 2 2= 16). For this reason, many experiments are restricted to two levels. Fractional factorial experiments further reduce the number of treatments to be executed in an experiment.

DOE Types

The following is a summary of some of the most common DOE types.

1 One Factor Designs

These are the designs where only one factor is under investigation, and the objective is to determine whether the response is significantly different at different factor levels. The factor can be *qualitative* or *quantitative*. In the case of qualitative factors (*e.g.* different suppliers, different materials, etc.), no extrapolations (*i.e.* predictions) can be performed outside the tested levels, and only the effect of the factor on the response can be determined. On the other hand, data from tests where the factor is quantitative (*e.g.* temperature, voltage, load, etc.) can be used for both effect investigation and prediction, provided that sufficient data are

available. **2 Factorial Designs**

In factorial designs, multiple factors are investigated simultaneously during the test. As in one factor designs, qualitative and/or quantitative factors can be considered. The objective of these designs is to identify the factors that have a significant effect on the response, as well as investigate the effect of interactions (depending on the experiment design used). Predictions can also be performed when quantitative factors are present, but care must be taken since certain designs are very limited in the choice of the predictive model. For example, in two level designs only a linear relationship between the response and the factors can be used, which may not be realistic.

General Full Factorial Designs

In general full factorial designs, each factor can have a different number of levels, and the factors can be quantitative, qualitative or both.

Two Level Full Factorial Designs

These are factorial designs where the number of levels for each factor is restricted to two. Restricting the levels to two and running a full factorial experiment reduces the number of treatments (compared to a general full factorial experiment) and allows for the investigation of all the factors and all their interactions.

If all factors are quantitative, then the data from such experiments can be used for predictive purposes, provided a linear model is appropriate for modeling the response (since only two levels are used, curvature cannot be modeled).

Two Level Fractional Factorial Designs

This is a special category of two level designs where not all factor level combinations are considered and the experimenter can choose which combinations are to be excluded. Based on the excluded combinations, certain interactions cannot be determined.

Plackett-Burman Designs

This is a special category of two level fractional factorial designs, proposed by R. L. Plackett and J. P. Burman, where only a few specifically chosen runs are performed to investigate just the main effects (*i.e.* no interactions).

Taguchis Orthogonal Arrays

Taguchis orthogonal arrays are highly fractional designs, used to estimate main effects using only a few experimental runs. These designs are not only applicable to two level factorial experiments, but also can investigate main effects when factors have more than two levels. Designs are also available to investigate main effects for certain mixed level experiments where the factors included do not have the same number of levels.

3 Response Surface Method Designs

These are special designs that are used to determine the settings of the factors to achieve an optimum value of the response.

4 Reliability DOE

This is a special category of DOE where traditional designs, such as the two level designs, are combined with reliability methods to investigate effects of different factors on the life of a unit. In Reliability DOE, the response is a life metric (*e.g.* age, miles, cycles, etc.), and the data may contain censored observations (suspensions, interval data). One factor designs and two level factorial designs (full, fractional, and Plackett-Burman) are available in **DOE++** to conduct a Reliability DOE analysis.

Optimization techniques in Pharmaceutical formulation and processing15-19 :

First of all it is necessary to understand the meanings of "Optimization". "to optimize" is to make as much perfect as possible. It is the process of obtaining optimum formulation.

According to Merriam Webster Dictionary Optimization means,"an act,or methodology of making something (as a design,system,or decision) as fully perfect,functional,or effective as possible;specifically : the mathematical procedures". Optimization techniques are the research analytical tools for a problem which are available to a researcher.These problems are related to pharmaceutical formulation,composition of the delivery system and process design.These involve mostly mathematical techniques in novel drug delivery systems. In Mathematics, optimization is the process of obtaining of maxima or minima.In most of the cases, Lagrangian method of optimization has been used for solving problems.There are certain variables in optimization techniques regarding Pharmaceutical formulations:

These variables are of two types:

1.Independent variables

2.Dependent variables

Fig:2- Response Surface in Optimization techniques of Pharmaceutical formulation and processing

There are two types of problem which are usually addressed in the optimization

techniques:

1. Unconstrained
2. Constrained

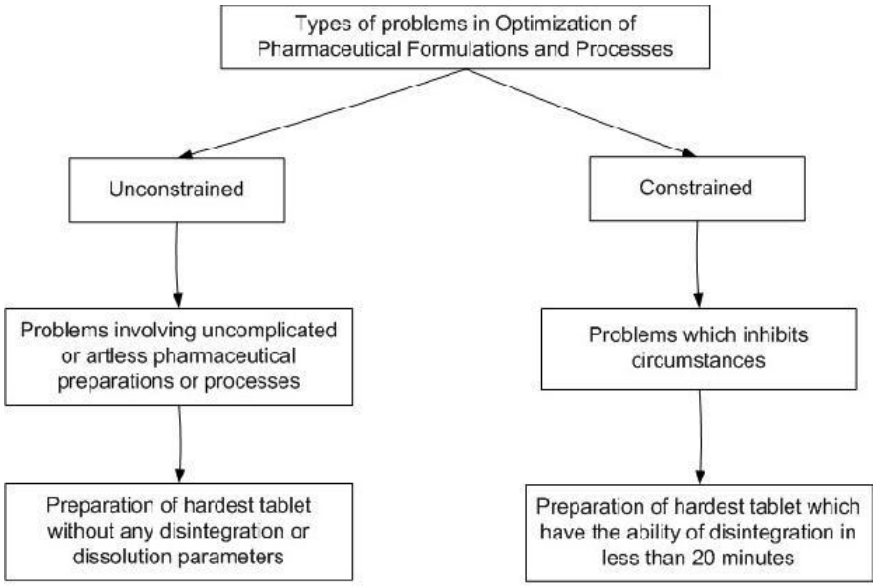


Fig :3-Types of problems in optimization

Methods for Optimization techniques:

Several methods can be of use in Applied optimization:

1. Evolutionary operations
2. The Simplex methods
3. The Lagrangian Method
4. Search Method
5. Canonical Analysis

Forms of Optimization techniques:

There are three forms of systematic optimization techniques

1. Sequential Optimization techniques.
2. Simultanuous Optimization techniques.
3. Combination of both.

1. Sequential Methods:

This method is alos referred to as the "Hill climbing method". As first of all a small number of experiments are done and further research will be done by using the increase or decrease of response. In this way a maximum or minimum will be reached i.e. an optimum solution.

2. Simultanuous Methods:

This method involves the use of full range of experiments by an experimental design and the results are than used to fit in the mathematical model. And maximum or minimum response will then be found through this fitted model.

Artificial Neural Network (ANN) and Optimization of Pharmaceutical formulations:

ANN has been entered in pharmaceutical studies to forecast the relationship between the response variables and causal factors. This relationship is non-linear relationship. ANN is most successfully used in Multi-objective simulatenous optimization problem. (Takayama K et al.) This problem arises when the favorable conditions of formulation for a single property may not be favorable for other characteristics.

Radial basis functional network (RBFN) is proposed for multi-objective simultaneous optimization problem (Anand P et al.). RBFN is an ANN in which activation functions are radial basis functions (RBF). RBF is a function whose value depends only on the distance from the center or origin.

Applications:

- Through the optimization of the micro-encapsulation parameters such as shape of microcapsules ,the strength of the micocapsule membranes and the membrane permeability of microcapsules now it is possible to develop more better forms of microcapsules for the treatment of diabetes and liver diseases.
- Optimization techniques are also helpful in reducing the time of experimentation, study of pharmacokinetic parameters and High performance liquid chromatographic analysis.
- One of the most important applications of Pharmaceutical optimization is found in the field of new drug discovery as the physicochemical and biological properties of a system can be improved by chemical modifications using Optimization technique.

Aim and objective

Fluconazole is triazole antifungal agent. It is used for the treatment of fungal infections.Conventional preparations of fluconazole overdoses may cause hallucinations and paranoid behaviour. Controlled release tablets will be a better alternation in reducing dose and increasing efficacy with reducing fluctuations.

So our study was aimed to design and development and optimization of tablets containing fluconazole as controlled release of drug for longer periods of time.By controlling the rate of release the over dose effects such as hallucinations and paranoid behaviour will also be minimized. So the objective was

- To prepare fluconazole tablet using different polymers for controlled release.
- Evaluate the effect of polymers and percentage drug release.
- To analyse the data statistically and optimize the formulation.

PLAN OF WORK

1. Pre-formulation studies.
2. Preparation of tablets by direct compression method.
3. Evaluation of tablets for:
    a. Hardness
    b. thickness
    c. Friability
    d. Weight variation
    e. Assay
    f. *Invitro*Dissolution studies.
    g. Anti microbial studies
    h. IR spectra studies
4. Kinetic models analysis
    a. First order
    b. Zero order
    c. Higuchi model
    d. Hixson-Crowell model
    e. Korsmeyer- Peppas model.
5. Experimental Design

6.Statistical Analysis

7.Optimization

Maderuelo.C et.al[20] developed model-independent approach to optimize the release kinetics of drugs from sustained-release formulations, using stavudine (d4T) as a model drug. This approach is based on the pharmacokinetic simulation of drug plasma levels through a semiparametric approach of the input function and on convolution with an empirical polyexponential unit impulse response function. Input functions were evaluated using different zero-order and first-order release constants. Optimum drug release to obtain a specific pharmacokinetic profile was approached using target model-independent pharmacokinetic parameters such as C(max)(SS), C(min)(SS), t(max)(SS), and peak-trough fluctuations. A Monte Carlo simulation was performed to estimate the fractional attainment of d4T plasma concentrations over therapeutic d4T levels. Zero-order (K(0) = 4 mg/h) and first-order (K(1) = 0.05 h(-1)) release constants were optimal for the formulation of sustained-release d4T tablets, plasma concentrations within the therapeutic range being achieved.

Prajapati .B.G et.al[21] formulated and evaluated statical influence different concentration of hydroxy propyl methyl cellulose K4M and ethyl cellulose on Propranolol hydrochloride release compression coated tablet using 3^2 full factorial design. Tablets were prepared by direct compression technique. Time controlled pulsatile Propranolol hydrochloride tablets containing 40 mg of Propranolol hydrochloride were developed using different ratio of hydroxypropyl methylcellulose and ethyl cellulose that retard the drug release in the physiological environment of stomach and 2-3 hr in intestine. Formulation was optimized on basis of acceptable tablet properties and *in vitro* drug release. To analyse the release mechanism of optimize batch zero order, first order, Higuchi, Hixson Crowell, Korsmeyer–Peppas kinetic model were used. The kinetics release of optimize batch F3 was best explained by zero order model, Hixson Crowell, and Korsmeyer–Peppas kinetic model.

MadgulkarARBhalekar et.al[22] designed sustained release matrix tablets of venlafaxine hydrochloride using ion exchange resin with the incorporation of hydrophilic and hydrophobic polymer combinations. Venlafaxine HCl was loaded onto Indion 244 by batch method and then resinate were wet granulated with ethyl cellulose and blended with hydroxypropylmethylcellulose and compressed. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile at 2 h and at 18 h. Hydroxypropylmethylcellulose and ethylcellulose were taken as the independent variables.

Response surface plots and contour plots were drawn, and optimum formulations were selected by feasibility and grid searches. Resinate shows inadequate sustained release profile. Compressed matrices exhibited the anomalous release mechanism, as the value of release rate exponent (n) varied between 08109 and 08719, resulting in regulated and complete release until 20hrs. Validation of optimization study, performed using five confirmatory runs, indicated very high degree of prognostic ability of response surface methodology, with mean percentage error as 1.152+/-1.88%. Regulated drug release study indicates that the hydrophilic and hydrophobic matrix tablets of venlafaxine resinate prepared using hydroxypropylmethylcellulose and ethylcellulose, can successfully be employed as a once-a-day oral controlled release drug delivery.

Madgulkar.A et.al[23] formulated buccal adhesive tablets of miconazole nitrate with prolonged antifungal activity. The simplex centroid experimental design was used to arrive at optimum ratio of carbopol 934P,hydroxypropylmethylcelluloseK4Mandpolyvinylpyrollidone, which will provide desired drug release and mucoadhesion. Swelling index, mucoadhesive strength and *in vitro* drug release of the prepared tablet was determined. The drug release and bioadhesion was dependent on type and relative amounts of the polymers. The optimized combination was subjected to *in vitro* antifungal activity, transmucosal permeation, drug deposition in mucosa, residence time and bioadhesion studies. IR spectroscopy was used to investigate any interaction between drug and excipients. Dissolution of miconazole from tablets was sustained for 6 h. based on the results obtained, it can be concluded that the prepared slow release buccoadhesive tablets of miconazole would markedly prolong the duration of antifungal activity. Comparison of *in vitro* antifungal activity of tablet with marketed gel showed that drug concentrations above the minimum inhibitory concentration were achieved immediately from both formulations but release from tablet was sustained up to 6 h, while the gel showed initially fast drug release, which did not sustain later. Drug permeation across buccal mucosa was minimum from the tablet as well as marketed gel; the deposition of drug in mucosa was higher in case of tablet. *In vitro* residence time and bioadhesive strength of tablet was higher than gel. Thus the buccoadhesive tablet of miconazole nitrate may offer better control of antifungal activity as compared to the gel formulation.

Raghavendrarao N.G et.al[24] formulated and evaluated sustained release matrix tablets of water soluble Tramadolhydrochloride using different polymers viz. Hydroxy propyl methyl

cellulose (HPMC) and natural gums likeKaraya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for thestudy. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rateswere modulated by combination of two different rates controlling material and triple mixture of three different ratecontrollingmaterial. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration andpolymer blend concentration were studied. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken.Dissolution data was analyzed by Korsmeyer-Peppas power law expression and modified power law expression. It was observed that matrix tablets contained polymer blend of HPMC/CG were successfully sustained the release of drug upto 12 hrs. Among all the formulations, formulation F16 which contains 20% HPMC K15M and 80% of CG,release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile of formulation F16 was comparable with the marketed product. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that Tramadol hydrochloride was stable in the matrix tablets. The DSC and FTIR study revealed that there was no chemical interaction between drug and excipients.

Bhalekar MR et.al[25] prepared a sustained release drug delivery system of venlafaxine hydrochloride by using a wax matrix system. The effects of bees wax and carnauba wax on drug release profile was investigated. A 3(2) full factorial design was applied to systemically optimize the drug release profile. Amounts of carnauba wax (X(1)) and bees wax (X(2)) were selected as independent variables and release after 12 h and time required for 50% (t(50)) drug release were selected as dependent variables. A mathematical model was generated for each response parameter. Both waxes retarded release after 12 h and increases the t(50) but bees wax showed significant influence. The drug release pattern for all the formulation combinations was found to be approaching Peppas kinetic model. Suitable combination of two waxes provided fairly good regulated release profile. The response surfaces and contour plots for each response parameter are presented for further interpretation of the results. The optimum formulations were chosen and their predicted results found to be in close agreement with experimental findings.

Madgulkar A et.al[26] formulated and evaluated sustained release mucoadhesive tablets of Itraconazole. It is practically insoluble in aqueous fluids hence its solid dispersion with Eudragit E100 was prepared by spray drying. This was formulated in matrix of hydrophilic mucoadhesive polymers Carbopol 934P (CP) and Methocel K4M (HPMC). The formulation was optimized using a 3(2) factorial design. Amounts of CP and HPMC were taken as formulation variables for optimizing response variables i.e. mucoadhesion and dissolution parameters. The optimized mucoadhesive formulation was orally administered to albino rabbits, and blood samples collected were used to determine pharmacokinetic parameters. The solid dispersion markedly enhanced the dissolution rate of itraconazole. The bioadhesive strength of formulation was found to vary linearly with increasing amount of both polymers. Formulations exhibited drug release fitting Peppas model with value of n ranging from 0.61 to 1.18.

Mandal U et.al[27] designed an oral sustained release matrix tablet of metformin HCl and to optimize the drug release profile using response surface methodology. Tablets were prepared by non-aqueous wet granulation method using HPMC K 15M as matrix forming polymer. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile. HPMC K 15M (X(1)) and PVP K 30 (X(2)) were taken as the independent variables. The dependent variables selected were % of drug released in 1 hr (rel(1 hr)), % of drug released in 8 hrs (rel(8 hrs)) and time to 50% drug release (t(50%)). Contour plots were drawn, and optimum formulations were selected by feasibility and grid searches. The formulated tablets followed Higuchi drug release kinetics and diffusion was the dominant mechanism of drug release, resulting in regulated and complete release within 8 hrs. The polymer (HPMC K 15M) and binder (PVP K 30) had significant effect on the drug release from the tablets ($p<0.05$). Polynomial mathematical models, generated for various response variables using multiple linear regression analysis, were found to be statistically significant ($p<0.05$). Validation of optimization study, performed using 8 confirmatory runs, indicated very high degree of prognostic ability of response surface methodology, with mean percentage error (+/-S.D.) 0.0437+/-0.3285. Besides unraveling the effect of the 2 factors on the *in vitro* drug release, the study helped in finding the optimum formulation with sustained drug release.

Sami Nazzal et.al[28] described the objective of this study was to evaluate the effect of some processing parameters on the release of lipid formulation from a tablet dosage form.A 17-run, face-centered cubic design was employed to evaluate the effect of colloidal silicates (*X*1), magnesium stearate mixing time (*X*2), andcompression force (*X*3) on flow, hardness, and dissolution of Coenzyme Q10 (CoQ10) lipid formulation from a tablet dosage form. The optimized formulation was subsequently subjected to a short-term accelerated stability study. All preparations had a flowability index values ranging from 77 to 90. The cumulative percent of CoQ10 released within 8 h (*Y*5) ranged from 40.6% to 90% and was expressed by the following polynomial equation: $Y5 = 49.78 - 16.36X1 + 2.90X2 - 3.11X3 - 0.37X1X2 + 1.06X1X3 - 1.02X2X3 + 11.98X21 + 10.63X22 - 7.10X23$. When stored at 4 ◦C, dissolution rates were retained for up to 3 months. Storage at higher temperatures, however, accelerated lipid release and caused leakage, and loss of hardness. Processing parameters have a profound effect on the release of lipid formulations from their solid carriers. While optimized controlled release formulations could be attained, further considerations should be made to prepare "liquisolids" that are physically stable at higher storage temperatures.

Huang YB et.al[29] investigated to develop propranolol extended releaseformulations containing hydroxypropylmethylcellulose (HPMC). The results indicate that the drug release from the tablet form containing a high amount of HPMC was incomplete, and avicel addition could increase the release percent at a later stage. In order to readily obtain an optimal formulation, response surface methodology and multiple response optimization utilizing a quadratic polynomial equation was used. The model formulations were prepared according to a factorial design. The effects of causal factors including the HPMC/drug ratio (X1) and avicel level (X2), on drug release were also measured. The drug release percentage at 1.5, 4, 8, 14 and 24 h were the target response and were restricted to not more than 25%, 35-50%, 55-70%, 75-90%, and 95-110%, respectively. The results showed that the optimized formulation provided a dissolution pattern equivalent to the predicted curve, which indicated that the optimal formulation could be obtained using response surface methodology. The mechanism of drug release from HMPC matrices tablets followed quasi-Fickian diffusion.

Philip Plumb.A et.al[30] investigated the effect of varying optimization parameters on the proposed optimum of a tablet coatingformulation requiring minimization of crack velocity and maximization of film opacity. An artificial neural network (ANN) comprising six input

and two output nodes separated by a single hidden layer of five nodes was trained using 100 pseudo-randomly distributedrecords and optimized by guided evolutionary simulated annealing (GESA). GESA was unable to identify a formulation that satisfied both 21 a crack velocity of 0 m s and a film opacity of 100% due to conflict centred on the response of the properties to variation in pigmentparticle size. Constraining film thickness exacerbated the property conflict. By adjusting property weights (i.e. the relative importance ofeach property), GESA was able to propose formulations that were either crack resistant or that were fully opaque.

Kozo Takayamaet.al[31] designed neural network based optimization of drug formulations. A pharmaceutical formulation is composed of several formulation factors and process variables. Several responses relatingto the effectiveness, usefulness, stability, as well as safety must be optimized simultaneously. Consequently, expertise andexperience are required to design acceptable pharmaceutical formulations. A response surface method (RSM) has widelybeen used for selecting acceptable pharmaceutical formulations. However, prediction of pharmaceutical responses based on the second-order polynomial equation commonly used in an RSM, is often limited to low levels, resulting in poor estimations of optimal formulations. The purpose of this review is to describe the basic concept of the multi-objectivesimultaneous optimization technique, in which an artificial neural network (ANN) is incorporated. ANNs are being increasingly used in pharmaceutical research to predict the nonlinear relationship between causal factors and responsevariables. Superior function of the ANN approach was demonstrated by the optimization for typical numerical examples.

Svetlana Ibric et.al[32] used generalized regression neural network (GRNN) in the design of extended-releaseaspirin tablets. As model formulations, 10 kinds of aspirin matrix tablets were prepared. EudragitRS PO was used asmatrix substance. The amount of EudragitRS PO and compression pressure were selected as causal factors. *In-vitro*dissolution–time profiles at four different sampling times, as well as coefficients *n* (release order) and log *k* (release constant)from the Peppas equation were estimated as release parameters. A set of release parameters and causal factors were used astutorial data for the GRNN and analyzing using a computer. A GRNN model was constructed. The optimized GRNN modelwas used for prediction of formulation with desired *in vitro* drug release. For two tested formulations there

was very goodagreement between the GRNN predicted and observed *in vitro* profiles and estimated coefficients. Calculated difference (f) 1and similarity (f) factors indicate that there is no difference between predicted and experimental observed drug release 2profiles. This work illustrates the potential for an artificial neural network, GRNN, to assist in development of extendedreleasedosage forms.

HisakadzuSunada et.al[33] prepared and evaluated rapidly disintegrating tablets using both direct compression and wet compression methods. Tablet properties, such as porosity, tensile strength, wetting time and disintegration time were evaluated, and the formation and disintegration mechanisms of the tablets were elucidated. Formulation and preparation conditions were optimized using polynomial regression orartificial neural network .

Paola Mura et.al[34] applied statistical experimental design to evaluate the influence of some process and formulation variables andpossible interactions among such variables, on didanosine release from directly-compressed matrix tablets based onblends of two insoluble polymers, Eudragit RS-PM and Ethocel 100, with the final goal of drug release behavior optimization. The considered responses were the percent of drug released at three determined times, the dissolutionefficiency at 6 h and the time to dissolve 10% of drug. Four independent variables were considered: tablet compression force, ratio between the polymers and their particle size, and drug content. The preliminary screeningstep, carried out by means of a 12-run asymmetric screening matrix according to a D-optimal design strategy, allowed evaluation of the effects of different levels of each variable. The drug content and the polymers ratio had the mostimportant effect on drug release, which, moreover, was favored by greater polymers particle size; on the contrary thecompression force did not have a significant effect. The Doehlert design was then applied for a response-surfacestudy, in order to study in depth the effects of the most important variables. The desirability function was used tosimultaneously optimize the five considered responses, each having a different target. This procedure allowedselection, in the studied experimental domain, of the best formulation conditions to optimize drug release rate.Theexperimental values obtained from the optimized formulation highly agreed with the predicted values. The resultsdemonstrated the reliability of the model in the preparation of extended-release matrix tablets with predictable drug release profiles.

Peter C. Schmidt et.al[35] prepared a rotatable central composite design to evaluate the effects of lubricants and compression force on the physical characteristics ofeffervescent tablets. Effervescent tablets lubricated with a combination of spray dried l-leucine and polyethylene glycol 6000 are preparedby direct compression and examined. Residual force, crushing strength and disintegration time are considered as response variables andrelated to the l-leucine and polyethylene glycol concentrations and to the compression force. The calculated models are used to assess theinfluence of the production factors on tablet properties. As increasing amounts of l-leucine, showing good lubricating properties, reduce thecrushing strength and prolong tablet disintegration, the l-leucine concentration is kept at a low level. An optimum tablet formulationcontains 2% l-leucine and 3% polyethylene glycol 6000. The tablets have a tensile strength of 0.47 MPa and disintegrate in less than 2 min. Predicted and experimental results are in agreement within a 95% CI.

Pao-Chu Wuet.al[36]optimized the pH-dependent release of nicardipine hydrochloride extended release formulationsby using simultaneously combination two hydrophilic polymers: hydroxypropylmethylcellulose (HPMC) and sodium alginate asretardant and avicel as additive. The constrained mixture experimental design was used to prepare systematic model formulationswhich were composed of three formulation variables: the content of HPMC (*X*1), avicel (*X*2), and sodium alginate (*X*3). Theresponse surface methodology (RSM) and multiple response optimization utilizing the polynomial equation were used to searchfor the optimal formulation with specific release rate at different time intervals and to quantify the effect of each formulationvariables. The drug release percent at 3, 6 and 12 h were the target responses and were restricted to 10–30% (*Y*3 h), 40–65% (*Y*6 h) and not less than 80% (*Y*12 h), respectively.The results showed that the effect of combination ofHPMCand sodium alginatewasthemost influence factor on the drug release from extended-release matrix tablets. The observed results of *Y*3 h, *Y*6 h and *Y*12 h coincided well with the predictions in the RSM optimization technique,indicating it was quite useful for optimizing pharmaceuticalformulation. The mechanism of drug release from extended-release matrix tablets was dependent on the added amount of alginate. The release kinetic of drug from HPMC matrix tablets with alginate was followed the zero-order release pattern.

Khan M..A et.al[37] aimed (1) to evaluate the effect of formulation ingredients on the release rate of Ubiquinone from its adsorbing solid compact; and (2) to prepare and evaluate an optimized self-nanoemulsifiedtabletformulation. A three factor, three-level Box–Behnken design was used for the optimization procedure, with theamounts of copolyvidone ($X1$), maltodextrin ($X2$) and microcrystalline cellulose ($X3$) as the independent variables. The response variable was cumulative percent of Ubiquinone emulsified in 45 min with constraints on weight, flowability index, tensile strength, friability and disintegration time of the dry powdered emulsion and the resultant compact.Based on the experimental design, different Ubiquinone release rates and profiles were obtained. Mathematicalequations and response surface plots were used to relate the dependent and independent variables. The regressionequation generated for the cumulative percent emulsified in 45 min was $Y6=64.10-12.32X1-4.36X2-25.53X3+6.99X1X2+3.97X1X3+9.70X2X3-8.98X1^2-16.22X2^2+17.10X3^2$. The optimization model predicted an 85.4% releasewith$X1$, $X2$ and $X3$ levels of 66.6, 560.1 and100, respectively. A new formulation was prepared according to these levels. The observed responses were in close agreement with the predicted values of the optimized formulation.

Sunil Jain et.al[38] carried their work on formulation and process optimization to eliminate pickingfrom market image tablets. A tablet formulation when compressed using market image tooling may cause picking of powder. A D-optimalstatistical experiment was designed to optimize the direct compression formulation and the process to alleviate picking of powder. The effects of levels of magnesium stearate, colloidal silicon dioxide (CSD), and lubrication time onpicking were investigated using original compression tooling. These optimization results provided a small robust manufacturing region, hence a change in the cut angles of embossed letters and numbers from 70° to 90° in themodified compression tooling was evaluated. A statistical analysis of the data identified a robust manufacturingregion that included formulations containing magnesium stearate 1–1.25% w:w, CSD 0.1–0.3% w:w, with alubrication time of 5–10 min when compressed using modified compression tooling. The results indicate a significantreduction in picking by increasing the cut angles of embossed letters and numbers in the modified compressiontooling. By evaluating interactions between various variables, we demonstrate a concentration dependent effect of CSD on the lubrication efficiency of magnesium stearate and compactability of microcrystalline cellulose

containingformulation. In addition, the lubrication efficiency of magnesium stearate is maintained by blending CSD withpowder blend prior to lubrication with magnesium stearate.

Julijana Kristl et .al[39] investigated the development of the floating matrix tablets, which after oral administrationare designed to prolong the gastric residence time, increase the drug bioavailability and diminish the side effects ofirritating drugs. The importance of the composition optimisation, the technological process development for thepreparation of the floating tablets with a high dose of freely soluble drug and characterisation of those tablets (crushing force, floating properties *in vitro* and *in vivo*, drug release) was examined. Tablets containing hydroxypropylmethylcellulose (HPMC), drug and different additives were compressed. The investigation shows that tabletcomposition and mechanical strength have the greatest influence on the floating properties and drug release. With theincorporation of a gas-generating agent together with microcrystalline cellulose, besides optimum floating (floating lagtime, 30 s; duration of floating, \8 h), the drug content was also increased. The drug release from those tablets wassufficiently sustained (more than 8 h) and non-Fickian transport of the drug from tablets was confirmed. Radiologicalevidence suggests that, that the formulated tablets did not adhere to the stomach mucus and that the mean gastric residence time was prolonged (\4 h).

Campisi.B et.al[40] Stated that in pharmaceutical industries, the formulator is usually faced with the optimisation of the excipient mixturecomposition aimed to prepare a product with the required characteristics. Experimental research methodologyrepresents an efficient approach for solving such optimisation problems. Planning mixture experiments using specificdesigns allows to analyse the blending properties of each mixture component and estimate an empirical modelapproximating the response of interest as a function of excipient proportions. In this study the evolution of theophylline solubility in a four-component system with constraints was analysed using two mixture designapproaches: a classical mixture component proportion approach and a mathematically independent variable approach. An optimal region characterised by high solubility values was found and further explored in order to verifythe insensitivity of theophylline solubility to slight variations of the excipient mixture composition.

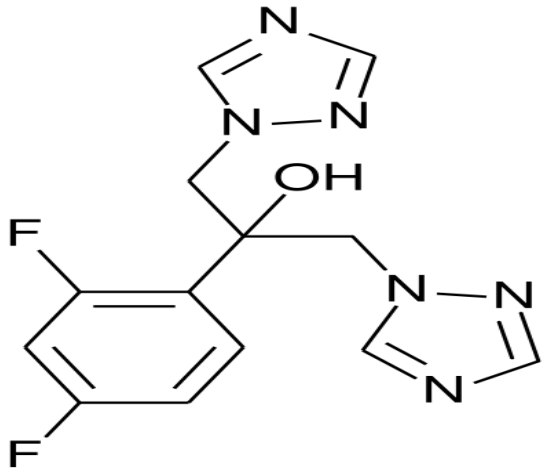
Adrian Bodea et.al[41] optimized hydrophilic matrix tablets using a D-optimal design.One method of achieving sustained drug release is by the use of hydrophilic polymeric excipients directly compressed with active ingredients into tablets. Hydrophilic polymers swell in the presence of water to form hydrogelstructures from which drugs are released by slow diffusion. The release rate modulation is obtained by the use ofdifferent types of polymer alone or in combinations. Optimization of the release rate of propranolol hydrochloride from mixturescontaining two hydrophilic polymers: hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose(CMCNa) was made by mixture design. Mixing ratios of the two polymers with the activeingredient were selected as formulation factors. Experimental results were examined using a D-optimal quadraticmodel. Contour plots were formed based on the model to assess the change in the response surface in order tounderstand the relationship between dependent and independent variables. The results enabled the formulation of tablets with the desired dissolution characteristics together with a fairly completecharacterization of the system.Optimization of release rate was performed applying constraints on the cumulative amounts of drug released after 1,6 and 12 h release time intervals. Optimized formulations presented release rates that were close to the predicted values. Fitting the release data from optimized formulations was performed according to Korsmeyer et al. (1983) andPeppas and Sahlin (1989) kinetic models. Release from optimized formulations occurs mainly by Fickian diffusion butan important fraction of the drug is released by polymer relaxation.

Kozo Takayama et.al[42] develop a multi-objective simultaneous optimization technique in which an artificial neuralnetwork (ANN) was incorporated. As model formulations, 18 kinds of Trapidil tablet were prepared. The amounts ofmicrocrystalline cellulose, hydroxypropyl methylcellulose and compression pressure were selected as causal factors. In orderto characterize the release profiles of Trapidil, the release order and the rate constant were estimated. A set of releaseparameters and causal factors was used as tutorial data for ANN and fed into a computer. Non-linear relationships betweencausal factors and the release parameters were represented well with the response surface of ANN. The simultaneous optimization of the sustained-release tablet containing Trapidil was performed by minimizing the generalized distancebetween the predicted values of each response and the optimized one that was obtained individually. The optimal formulations gave satisfactory release profiles,

since the observed results coincided well with the predicted results. Thesefindings demonstrate that a multi-objective optimization technique incorporating ANN is quite useful in the optimization ofpharmaceutical formulations.

FLUCONAZOLE[43]

Structure :



Chemical Formula : $C_{13}H_{12}F_2N_6O$

IUPAC Name : 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol

Weight : 306.2708

Description : Fluconazole is a white crystalline solid which is slightly soluble in water and saline.

PHARMACOLOGY :

Mechanism of action : Fluconazole interacts with 14-α demethylase, a cytochrome P-450 enzyme necessary to convert lanosterol to ergosterol. As ergosterol is an essential component of the fungal cell membrane, inhibition of its synthesis results in increased cellular permeability causing leakage of cellular contents. Fluconazole may also inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeasts to

mycelial forms, inhibit purine uptake, and impair triglyceride and/or phospholipid biosynthesis.

Pharmacodynamics : Fluconazole, a synthetic antifungal agent of the imidazole class, is used to treat vaginal candidiasis. It inhibits the fungal lanosterol 14 alpha-demethylase which thereby prevents the formation of ergosterol which is an essential component in the fungal cell membrane.

Protein binding : 11 to 12%

Metabolism : Hepatic

Route of elimination : In normal volunteers, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug.

Half life : 30 hours (range 20-50 hours)

Clearance : 0.23 mL/min/Kg [adults]

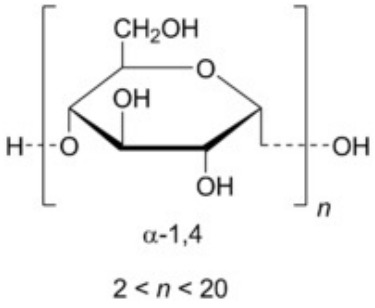
SIDE EFFECTS :

Nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice(yellowing of the skin or eyes),fever, chills, body aches, flu symptoms.
severe blistering, peeling, and red skin rash,easy bruising or bleeding, unusual weakness.

Toxicity :Symptoms of overdose include hallucinations and paranoid behavior.

MALTODEXTRIN[44]

1. Structure :



2. Chemical Name : Maltodextrin

3.Empirical Formula : (C6H10O5)n_H2O

4. Molecular Weight : 900–9000

5. Description : Maltodextrin occurs as a nonsweet, odorless, white powder or granules. The solubility,hygroscopicity, sweet and compressibility of maltodextrin increase as the DE increases

6. Functional Category : Coating agent; tablet and capsule diluent; tablet binder; viscosity increasing agent.

7.Uses :

Use Concentration (%)

Tablet binder (direct compression) 2–40

Tablet binder (wet granulation) 3–10.

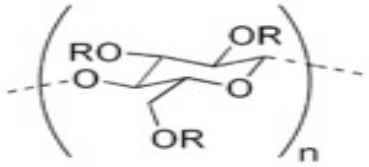
8. Applications :Maltodextrin is used in tablet formulations as a binder and diluent in both direct-compression and wet-granulation or agglomeration processes. Maltodextrin is also widely used in confectionery and

food products, as well as personal care applications.

9. Incompatibilities : Under certain pH and temperature conditions maltodextrin may undergo Maillard reactions with amino acids to produce yellowingor browning. Incompatible with strong oxidizing agents

HYDROXY PROPYL METHYL CELLULOSE[45]

1.Structure :



R = H or CH_3 or $CH_2CH(OH)CH_3$

2. Chemical Name : Cellulose hydroxypropyl methyl ether

3. Molecular Weight : Molecular weight is approximately 10 000–1 500 000.

4. Description : Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder

5.Solubility : Soluble in cold water, practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.

6.Melting point : 190–2008C;

7. Functional Category : Bioadhesive material; coating agent; controlled-release agent; dispersing agent; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

8. Applications : Hypromellose is widely used in oral, ophthalmic, nasal, and Topicalpharmaceutical formulations. In oral products,

hypromellose is primarily used as a tablet binder,in film-coating,(and as a matrix for use in extended release tablet formulations.

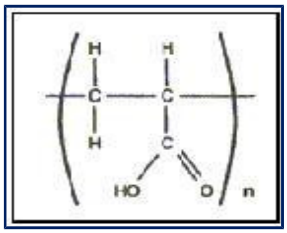
9. Incompatibilities : Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

CARBOPOL-940[46]

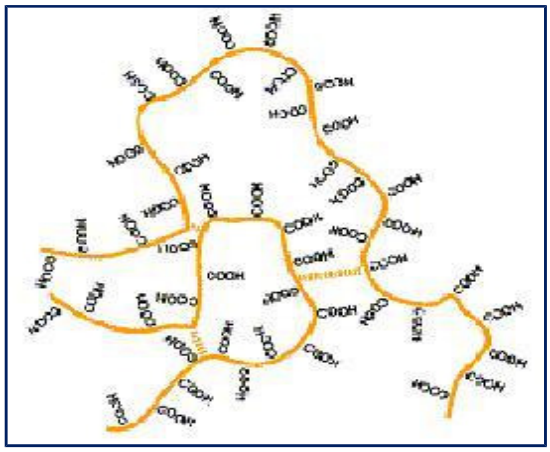
Chemical Name : Polyacrylate – 1- cross polymer.

Empirical Formula : Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol.

Structural Formula : General Structure of Carbopol Polymers



Schematic drawing of a molecular segment of a cross-linked polyacrylic acid polymer



Description : Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a characteristic slight odor.

Solubility : Swellable in water and glycerin and, after neutralization, in ethanol (95%).

Functional Category : Bioadhesive material; controlled-release agent; emulsifying agent; emulsion stabilizer; rheology modifier; stabilizing agent; suspending agent; tablet binder.

Applications in Pharmaceutical Formulation:

Use	**Concentration (%)**
Emulsifying agent	0.1 – 0.5
Gelling agent	0.5 – 2.0
Suspending agent	0.5 – 1.0
Tablet binder	0.75 – 3.0
Controlled-release agent	5.0 – 30.0

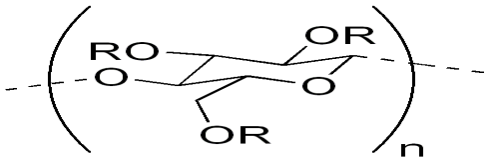
Table 1-Application of carbopol 940

Safety :

Carbomers are used extensively in nonparenteral products,particularly topical liquid and semisolid preparations. Gradespolymerized in ethyl acetate may also be used in oral formulations. There is no evidence of systemic absorption ofcarbomer polymers following oral administration.

ETHYL CELLULOSE[47]

1.structure :



R = H or CH_2CH_3

2. Chemical Name : Cellulose ethyl ether

3. Empirical Formula : C12H23O6(C12H22O5)

4. Description : Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.

5.Solubility : Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water

6. Functional Category : Coating agent; flavoring agent; tablet binder; tablet filler; viscosityincreasing agent.

7.uses : Use Concentration (%)
Sustained-release tablet coating 3.0–20.0

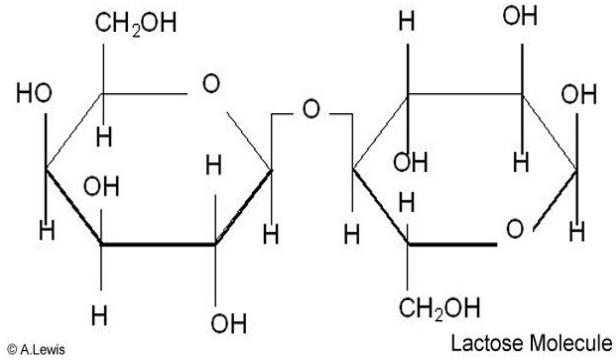
8 Applications : Ethylcellulose is widely used in oral and topical pharmaceutical formulations.The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose is additionally used in cosmetics and food products.

9. Incompatibilities :

Incompatible with paraffin wax and microcrystalline wax.

LACTOSE[48]

1. structure :



2. Chemical Name : O-b-D-Galactopyranosyl-(14)-b-D-glucopyranose

3. Empirical Formula : C12H22O11

4. Molecular Weight : 342.30

5. Description : Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b- lactose and anhydrous a-lactose. Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose.

6.Solubility : Soluble in water; sparingly soluble in ethanol (95%)and ether.

7. Functional Category : Directly compressible tablet excipient; dry powder inhaler carrier; lyophilization aid; tablet and capsule diluent; tablet and capsule filler.

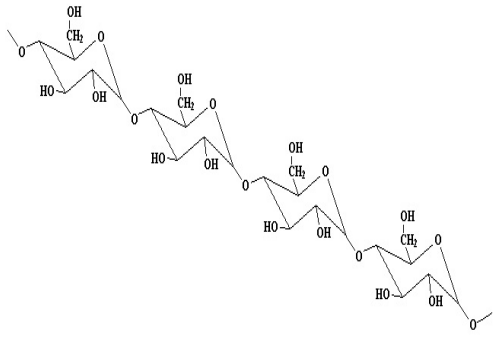
8. Applications : Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder.

Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous injections.

9. Incompatibilities : Lactose anhydrous is incompatible with strong oxidizers.

STARCH[49]

1. Structure :



2. Chemical Name : Starch

3. Empirical Formula : (C6H10O5)

4.Molecular Weight : 300–1000.

5. Description : Starch occurs as an odorless and tasteless, fine, white to off- white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

6. Solubility : Practically insoluble in cold ethanol (96%) and in cold Water.

7. Functional Category : Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.

8. Applications : Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent,and disintegrant.Specific starch varieties with a high amylose content (resistant starches) are used as insoluble fiber in clinical nutrition, and also for colon-targeting applications.

9. Incompatibilities : Starch is incompatible with strongly oxidizing substances.

Colored inclusion compounds are formed with iodine.

TALC[50]

1. Chemical Name : Talc

2. Empirical Formula : Mg6(Si2O5)4(OH)4.

3. Description : Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

4.Solubility : Practically insoluble in dilute acids and alkalis, organic solvents, and water.

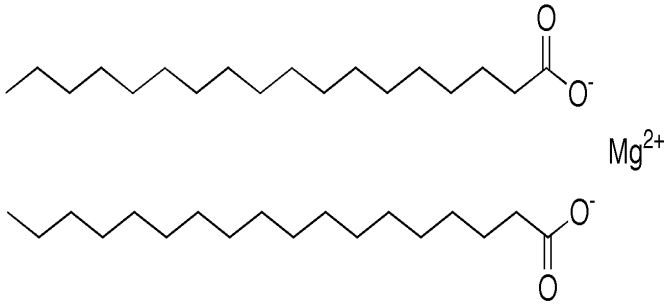
5. Functional Category : Anticaking agent; glidant; tablet and capsule diluent, tablet and capsule lubricant.

6. Applications : Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. However, it is widely used as a dissolutionretardant in the development of controlled-release products.Talc is also used as a lubricant in tablet formulations.

7. Incompatibilities : Incompatible with quaternary ammonium compounds.

MAGNESIUM STEARATE[51]

1.structure :



2. Chemical Name : Octadecanoic acid magnesium salt.

3. Empirical Formula : C36H70MgO4

4.Molecular Weight : 591.24

5 Structural Formula : [CH3(CH2)16COO]2Mg

6. Description : Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to thetouch and readily adheres to the skin.

7.Functional Category : Tablet and capsule lubricant.

8. Applications : Magnesium stearate is widely used in cosmetics, foods, And pharmaceuticalformulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.2 and 5.0% w/w. It is also used in barrier creams.

9. Incompatibilities : Incompatible with strong acids, alkalis, and iron salts

MATERIALS AND METHODS

Table-2: Instruments used

INSTRUMENTS	SUPPLIER/ MANUFACTURER
Single pan analytical balance	Shimadzu corporation Ltd - Japan
Tablet punching machine	(Rimek – MINI PRESS – II MT), Karnavati engineering Ltd - Gujarat
Pfizer hardness tester	Shreeji scientific & laboratory instruments Ltd - Mumbai
Roche friabilator	(Thermonik C-FTA20), Campbell electronics Ltd –Mumbai
Tap density apparatus	(Thermonik C-TDA2), Campbell electronics Ltd –Mumbai
Vernier calliper	Electro labs Ltd - Mumbai
Dissolution apparatus	(Thermonik DRS-8), Campbell electronics Ltd –Mumbai
Stability chamber	Technico Ltd - Mumbai
UV spectrophotometer	Shimadzu corporation Ltd - Japan

Table-3: Materials used

MATERIAL	SUPPLIER/ MANUFACTURER
Fluconazole (gift sample)	Aurobindo labs.ltd-Hyderabad
Carbopol-940	Otto kemi.ltd - Mumbai
HPMC	Lobachemie.ltd - Mumbai
Ethyl cellulose	SD fine chemicals.ltd - Mumbai
Maltodextrin	Mylan laboratories.ltd-Hyderabad
Starch	SD fine chemicals.ltd - Mumbai
Lactose monohydrate	SD fine chemicals.ltd - Mumbai
Talc	SD fine chemicals.ltd - Mumbai
Magnesium stearate	Lobachemie.ltd - Mumbai

MATERIALS AND METHODS

METHODOLOGY:

A. Determination of λ max:

Absorption spectra of Fluconazole:

a) A stock solution of 1mg/ml of Fluconazole was prepared by dissolving 100 mg of drug in small quantity of buffer of P^H 6.8 and sonicated for five min and diluted with buffer of P^H 6.8.

b) The stock solution was serially diluted to get solutions in the range of 2-10 µg/ml and λ max of the solution was found out from 200 - 400 nm.

c) The λ max of the solution was found to be 260 nm.

B. Determination of Standard Curve:

a) A stock solution of 1mg/ml of Fluconazole was prepared by dissolving 100 mg of drug in small quantity of distilled water and sonicated for five min and diluted with 100 ml of distilled water.
b) The stock solution was serially diluted to get solutions in the range of 2-10 µg/ml and λmax of the solution was found out.
c) The absorbance of the different diluted solutions was measured in a UV spectrophotometer at 260 nm.
d) A calibration curve was plotted by taking Concentration of the solution in g on X-axis and absorbance on Y-axis and Correlation Coefficient "r" was calculated.

PREPARATION OF POWDER BLEND:

The ingredients were accurately weighed and sifted through sieve #60, and then the materials except talc and magnesium stearate were blended using mortar and pestle for 10 min in an ascending order. Powder mixture then lubricated with talc and magnesium stearate for 5 min.

Formulation of controlled release Tablets:

Controlled release tablets were formulated by direct compression technique. In direct compression method Fluconazole and respective polymer of each formulation were mixed separately in a mortar. Each batch of tablets is prepared using two various polymers as four formulations in the ratios 1:1, 1:2, 2:1,2:2 . The lubricant was added to the powder mixture and mixed for another 2-3 min by hand. The powder mixture was directly compressed in single station tablet punching machine using talc and Magnesium stearate as a lubricant. The punched tablet weight about 200 mg (±25mg) and measured 4 mm in diameter punch.

Table-4 : Formulation Scheme of Fluconazole Controlled Release tablets(each ingredients in mg)

Formulation code	Fluconazole	Maltodextrin	HPMC	Carbopol 940	Ethyl Cellulose	Starch	Lactose	Talc	Magnesium stereate	Total weight (mg)
MH1	100	20	20	-	-	28	28	2	2	200
MH2	100	20	40	-	-	16	16	2	2	200
MH3	100	40	20	-	-	16	16	2	2	200
MH4	100	40	40	-	-	8	8	2	2	200
CH1	100	-	20	20	-	28	28	2	2	200
CH2	100	-	40	20	-	16	16	2	2	200
CH3	100	-	20	40	-	16	16	2	2	200
CH4	100	-	40	40	-	8	8	2	2	200
CE1	100	-	-	20	20	28	28	2	2	200
CE2	100	-	-	20	40	16	16	2	2	200
CE3	100	-	-	40	20	16	16	2	2	200
CE4	100	-	-	40	40	8	8	2	2	200
HE1	100	-	20	-	20	28	28	2	2	200
HE2	100	-	20	-	40	16	16	2	2	200
HE3	100	-	40	-	20	16	16	2	2	200
HE4	100	-	40	-	40	8	8	2	2	200

EVALUATION OF POWDER BLEND:

The prepared powder blends were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia[52] like Angle of repose, Bulk density, Tap density, Compressibility index &Hausner's ratio.

DRUG-EXCIPIENT COMPATABILITY STUDY BY FTIR:

IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymers. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 6 tons pressure. It was then scanned from 4000 to 400 cm^{-1} in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers; matching was done to detect any appearance or disappearance of peaks.

Angle of repose:

The angle of repose is the maximum angle formed between the surface of a pile of powder and horizontal surface. It is determined by the funnel method. A funnel was kept vertically at a specified height and the funnel bottom was closed. 10 gm of sample powder was filled inside the funnel. Then funnel was opened to release the powder to form a smooth conical heap which just touches the tip of the funnel. From the powder cone, the radius of the heap (r) and the height of the heap (h) were measured. The angle of repose is represented as 'θ' and calculated using the following equation:

$$\mathbf{Tan\ \theta = h/r}$$

Table-5: Flow properties and corresponding Angles of repose

FLOW PROPERTY	ANGLE OF REPOSE (DEGREES)
Excellent	25-30
Good	31-35

Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

Bulk Density:

The bulk densities of the powder blends were determined by transferring an accurately weighed 10 gm of sample powder to the graduated 50 ml measuring cylinder. The initial volume (bulk volume) was noted. The bulk density calculated using formula:

Bulk Density = Weight of Sample / Bulk Volume

Tapped Density:

An accurately weighed 10 gm of sample powder was transferred to the graduated 50ml measuring cylinder and placed on the tap density test apparatus. The apparatus was operated for a fixed number of taps (500 taps). The final volume (tapped volume) of the powder mass was noted. The tapped density calculated using formula:

Tapped Density = Weight of Sample/ Tapped Volume

Compressibility Index:

The compressibility index is determined from the bulk volume and tapped volume of the powder. The basic method used for the determination of compressibility index is to measure the bulk volume and the final tapped volume after tapping until no change in volume occurs. It is represented in percentage.

% Compressibility = (Tapped density - Bulk density) / Tapped density X 100

Table-6: Scale of Flowability based on Compressibility Index

COMPRESSIBILITY INDEX (%)	FLOW CHARACTER

≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very, very poor

Hausner's Ratio:

Hausner's ratio is the ratio of bulk density to the tapped density of powder (or) initial volume of the powder mass to the final volume of the powder mass obtained after specified number of tapping.

Table-7: Scale of Flowability based onHausner's Ratio

HAUSNER'S RATIO	FLOW CHARACTER
1-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very, very poor

EVALUATION OF CONTROLLED RELEASE TABLET:

Weight variation test:

20 tablets were selected randomly and weighed. Average weight was calculated. Each tablet was weighed individually. Weight of the individual tablets was compared with the average weight and reported with standard deviation. Since the tablets weighed more 200mg, Indian

Pharmacopoeia specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 7.5%.

Table-8:Weightvariation limit as per Indian Pharmacopoeia

Percentage deviation allowed under weight variation test	
Average weight of tablet	**Percentage deviation**
≤ 80mg	10%
80-250mg	7.5%
≥ 250mg	5%

Thickness and diameter:

Thickness is measured during tablet compression using Verniercalliper.

Hardness:

Hardness of the tablets were measured using Pfizer tablet hardness tester. A sample of 5 tablets were randomly taken from each batch and were held vertically in between the jaws which were pressed with hand until the tablet broken. The reading was noted from the needle of pressure dial which may be expressed in kilograms.

Friability:

Friability is performed to evaluate the ability of tablet to withstand abrasions. Ten tablets were weighed and placed in the tumbling chamber which was rotated for 100 revolutions. The tablets were dedusted and again weighed. The loss in weight indicated the friability.

$$\% \text{ Friability} = \frac{A-B}{B} \times 100$$

Where A=Initial weight of tablet

B=Weight of tablet after 100 revolutions.

Assay of tablet :[53]

Weigh 20 tablets and powder them. Take powdered tablet equivalent to 0.011gm i.e. about 0.16gm in 100ml of beaker which is previously dried. Add 50ml of chloroform in it. Keep it on ultrasonic bath for 15-20 min with slight heating then filter the chloroform in another dry beaker and evaporate chloroform to dryness. After evaporation make dilution with distilled warer to 10ml by rinsing the beaker. The absorbance of the diluted solution was then measured at 260nm using distille wateras the blank solution. The assay value is calculated by using the formula:

$$\textbf{Assay} = \frac{\textit{Test reading}}{\textit{Standard reading}} \times \frac{\textit{Wieght of standard}}{\textit{Weight of test}} \times 100$$

***In vitro* Dissolution studies:**

The drug release from different formulations were determined using a USP XIX Paddle apparatus under sink condition.The dissolution medium was 900 ml buffer 0.1NHCL for 2 hours followed by buffer of P^H 6.8 at 37± 0.2^0 C,up to 8hrs of the study, paddle speed of 50 rpm ,sample(5ml) was withdrawn at predetermined time intervals,and replaced by an equal volume of dissolution medium.Drug content in the dissolution sample was determined by UV spectrophotometer at 260nm.

***In vitro* Dissolution studies: Parameters**

Instruments : USP XIX Dissolution rate test apparatus

Type : Paddle

Medium : 900 ml

Temperature : 37± 0.2^0c.

RPM : 50

Duration : 8hr

Sampling time : 1 hr

Amount withdrawn : 5ml

λmax : 260nm

ANTIMICROBIAL STUDIES[54]

In microbial assay response of a growing populations of microorganisms in the antimicrobial environment is measured.The usual method involves agar diffusion assays in which the drug diffusion to agar seeded with a suseptible microbial population produce a zone of inhibition of growth in the commonest for samles to be assayed or applied in same form of reservoir to this layer agar sealed with indication organisms.The drug diffusion in to the medium and after incubation zone of growth inhibition forms.

In this antibiotic standard at different cocentration are incorporated in to liquid media to extend the growth inhibition of test organism is measured using turbidometrically using a saphalometer. The diameter of this test or unknown reflects the concentration of the compound being assayed,and it is compared with similar zones produced by various known concentrations of standard or reference compound.

In this technique assay the agar medium in a petridish is inoculated with the test organism *(mesonidinium rubrum).* The drug diffuses through agar anda zone of inhibition produced is measured.

ASSAY

Diffusional assays are carried out on a solid medium, usually an agar medium, which is suitable for growth of the test organism.The compound to be assayed is allowed to diffuse through the medium in a radial fashon from a pad or cup so that the adjacent growth of the test organism is either stimulated, as with growth factor .In this experiment test organism used for testing is *mosonodinium rubrum* a fungus.

The diameter of this area reflects the concentration of the compound being assayed,and it is compared with similar zones produced by various known concentrations of standard or reference compound.The diameter of the standard are plotted against logarithms of the concentrations used,and the linear portion of this standard curve is used for determining the actual concentration of the sample being assayed.

There are two types of diffusion assay and, although somewhat similar, each has its own particular advantages.

1.Cylinder Method

2. Paper Disc Method

DRUG RELEASE KINETICS[55-57]:

To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted in various kinetic models: zero order (Equation 6) as cumulative amount of drug released vs. time, first order (Equation 7) as log cumulative percentage of drug remaining vs. time, and Higuchi's model (Equation 8) as cumulative percentage of drug released vs. square root of time.

$$\mathbf{C = K_0\, t}$$

Where,

K_0:is the zero-order rate constant expressed in units of concentration/time

t: is the time in hours.

A graph of concentration vs. time would yield a straight line with a slope equal to K_0

and intercept the origin of the axes.

LogC = LogCo– kt/2.303

Where,

C_0:is the initial concentration of drug,

K: is the first order constant, and **t** is the time.

$Q = Kt^{1/2}$

Where,

K: is the constant reflecting the design variables of the system

t: is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted using the Hixson-Crowell cube root law (Equation 9):

$$3\sqrt{Q_0} - 3\sqrt{Q_t} = kHC\text{-}t$$

Where,

Q_t is the amount of drug released in time **t**,

Q_0 is the initial amount of the drug in the tablet, and

KHC is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix vs. time.

Mechanism of Drug Release[58]:

To evaluate the mechanism of drug release from Propranolol Hydrochloride floating matrix tablet, data of drug release were plotted in Korsmeyeretal'sequation (Equation 10) as log

cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line.

$$\mathbf{Mt-M\infty = Kt^n}$$

Where,

Mt/M∞is the fractional solute release,

t is the release time,

K is a kinetic constant characteristic of the drug/ polymer system, and

n is an exponent that characterizes the mechanism of release of tracers.

Exponent n values		**drug release mechanism**
0.45	0.43	Fickian diffusion
0.45< n <0.89	0.43< n <0.85	Anomalous transport
0.89	0.85	Case II transport.

EXPERIMENTAL DESIGN[59] :

Factorial design is an experimental design technique, by which the factor involved and their relative importance can be assessed. In the present study, the formulations, which are designed based on 2^2 full factorial design containing 2 factors evaluated at two levels and the experimental trials were performed at all possible combinations. Hardness, time to release 1st hour, time(in hrs) taken to release T50%,zone of inhibition were taken as dependent variables and values were fitted to SPSS statistics 17.0.

- The 2^2 full factorial design was considered and according to the model totally 16 experiments were conducted,from which four selected formulations were choosen for the study of optimization.

- Experiment designed by 2^2 factorial design,producing 4 factorial points.This design generally involves dependent variables Y,independent variable X.Two independent variable selected for this study were X1,amount of maltodextrin,X2,amount of Carbopol 940, X3,amount of HPMC , X4,amount of ethyl cellulose.The dependent variable were Y1,amount of drug release at 8^{th} hour;Y2,Zone of inhibition.

The two formulation variables evaluated include:

Factor A: Independent variables X1-X4 taken based on different ratios of polymers in milligrams (Matlodextrin:HPMC,Carbopol 940:HPMC, Carbopol940 :Ethyl Cellulose, HPMC:Ethyl Cellulose in the ratios 1:1,1:2,2:1,2:2)

Factor B: Dependent variables Y1,Y2 taken based on amount of drug released at 8th hour(Y1),Zone of Inhibition(Y2).

Statistical Analysis :

The effect of formulation variable on the response variable was statistically evaluated by applying ANOVA.The design was evaluated by quadratic model.

$$Y=b0+b1X1+b2X2 + b3X3+ b11X1^2+b22X2^2 +B33X3^2 +b12X1X2+ B13X1X3 +b23X2X3$$

Where Y is the response variable, bo is the constant and b1,b2,b3...etc are the regression coefficients of formulation variable.X1,X2 and X3 stand for main effect;X1X3,X2X3and X1X2 are interaction term.$X1^2$,$X2^2$ and $X3^2$ are quadratuc terms of the independent variable to evaluate nonlinearity.

Optimization[60] :

The final optimized formula was found after analyzing the response variable Y1 and Y2.The ANOVA study of each response variable yielded the best fitting polynomial model for that variable.The target of percentage release and zone of inhibition set at minimum and given equal weightage to both responses for optimization.By numerical optimization theoritically optimized formula with its percentage release and zone of inhibition were found out and compared with obtained in the experiments.

RESULTS & DISCUSSION

1.Determination of λ_{max} of of fluconazole

Fluconazole showed absorbance maxima at 260nm.

2.Calibration curve of Fluconazole

Calibration curve of fluconazole were plotted by measuring the absorbance of standard drug solution containing 1 to 10 µg/ml by UV spectrophotometer at 260nm.Calibration curve shows good linearity with R^2 value 0.996 using 0.1N HCL,R^2 value0.999 using buffer of P^H 6.8.

Table-9:Calibration curve Data of Fluconazole in 0.1N HCL at 260nm:

Concentration (µg/ml)	Absorbance at 260 nm
0	0
2	0.0525
4	0.0986
6	0.1625
8	0.2164
10	0.2817

Fig.4: Calibration curve of Fluconazole in 0.1N HCL at 260nm

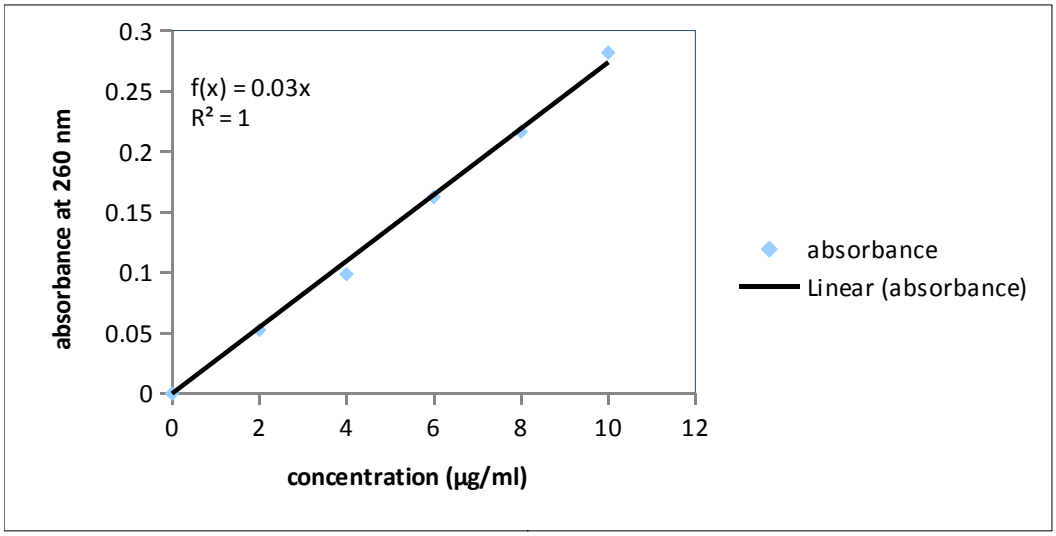


Table 10 :Caliberation Curve data of Fluconazole in buffer P^H 6.8 :

Concentration(µg)	Absorbance (260nm)
0	0
2	0.046
4	0.084
6	0.128
8	0.172
10	0.211

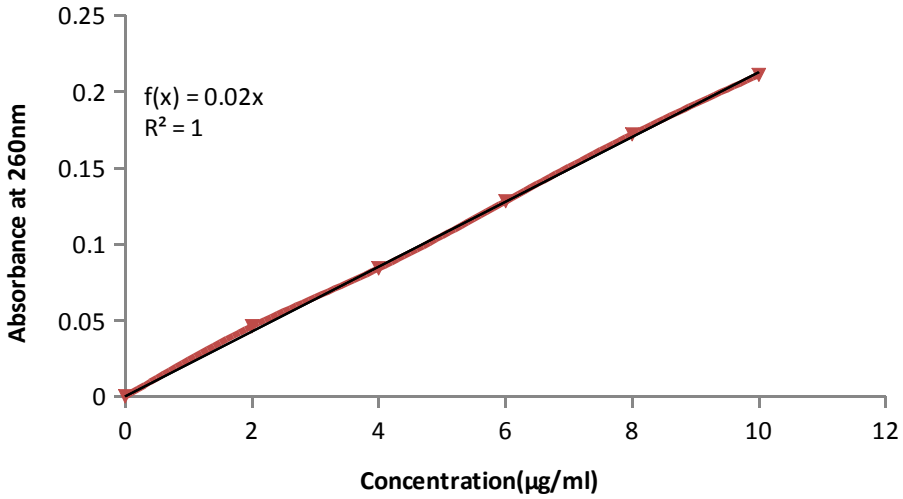


Fig.5 :Calibration curve of Fluconazole in buffer P^H6.8 at 260nm

3. IR SPECTRA:

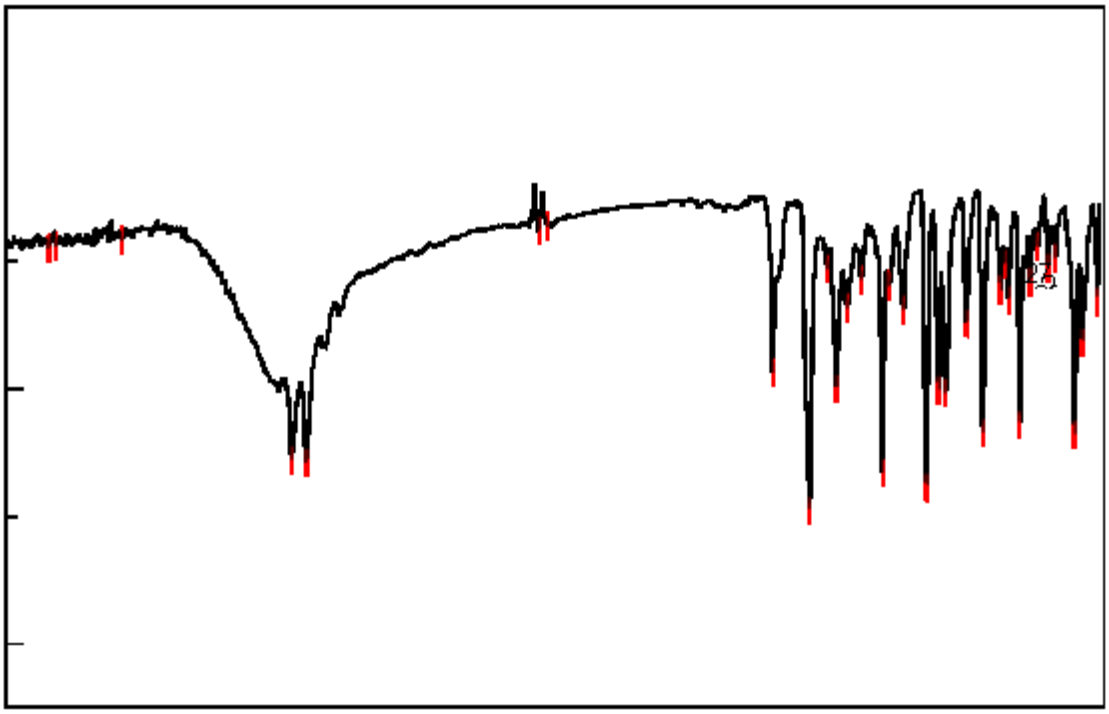
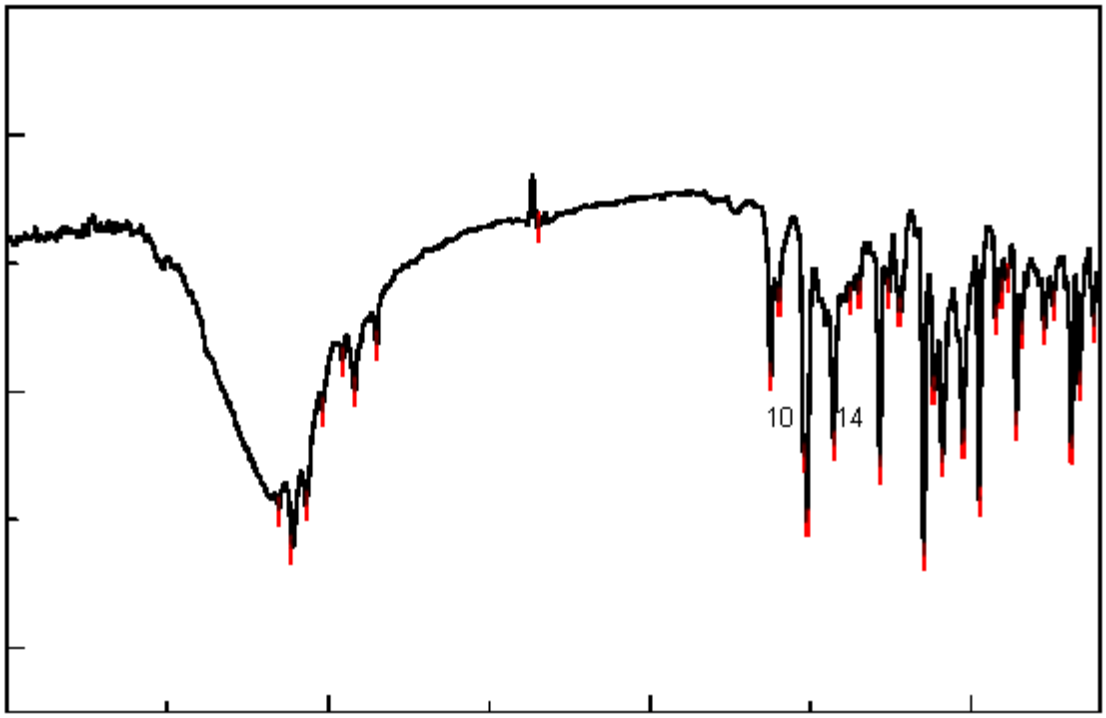
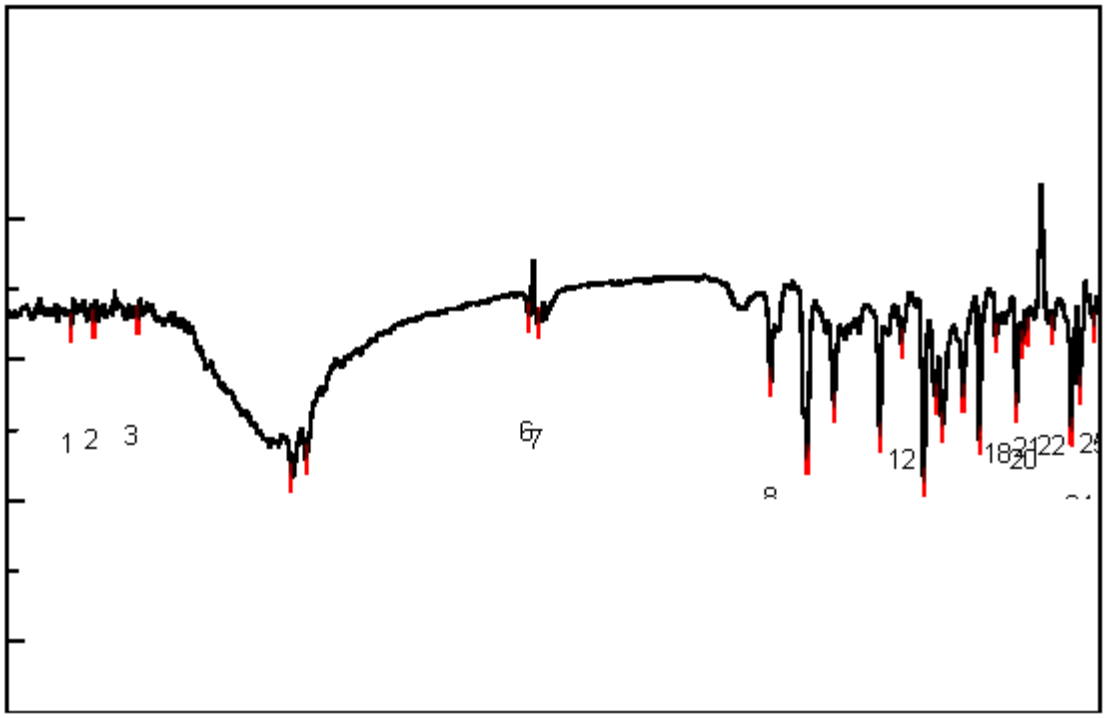
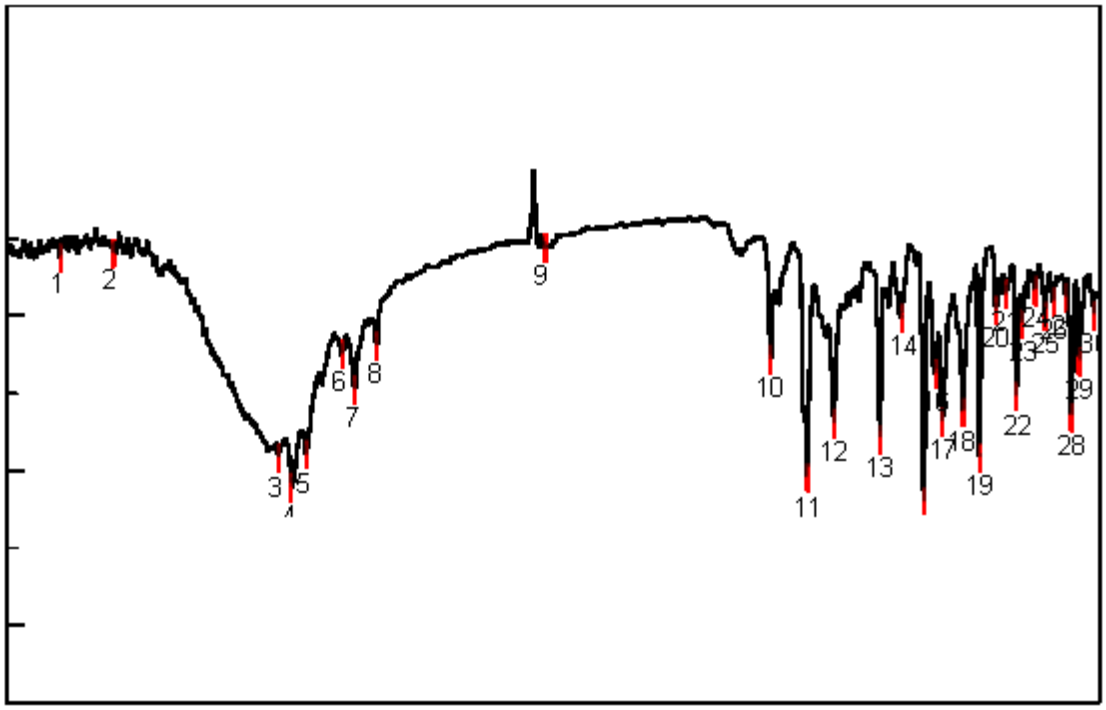


Table 11 : Interpretation of studied FTIR peaks with their characteristics functional groups

S.No	Peaks	Characteristic functional group
1	2926-2853	**CH2 CH Stretching**
2	1140	**C-O Stretching of Alcohol**
3	1419-1342	**OH Bending vibration**
4	1504	**C=N Stretching**
5	1079	**C-F Stretching**


10
14


1 2 3
6 7
12
18
20
21
22


1
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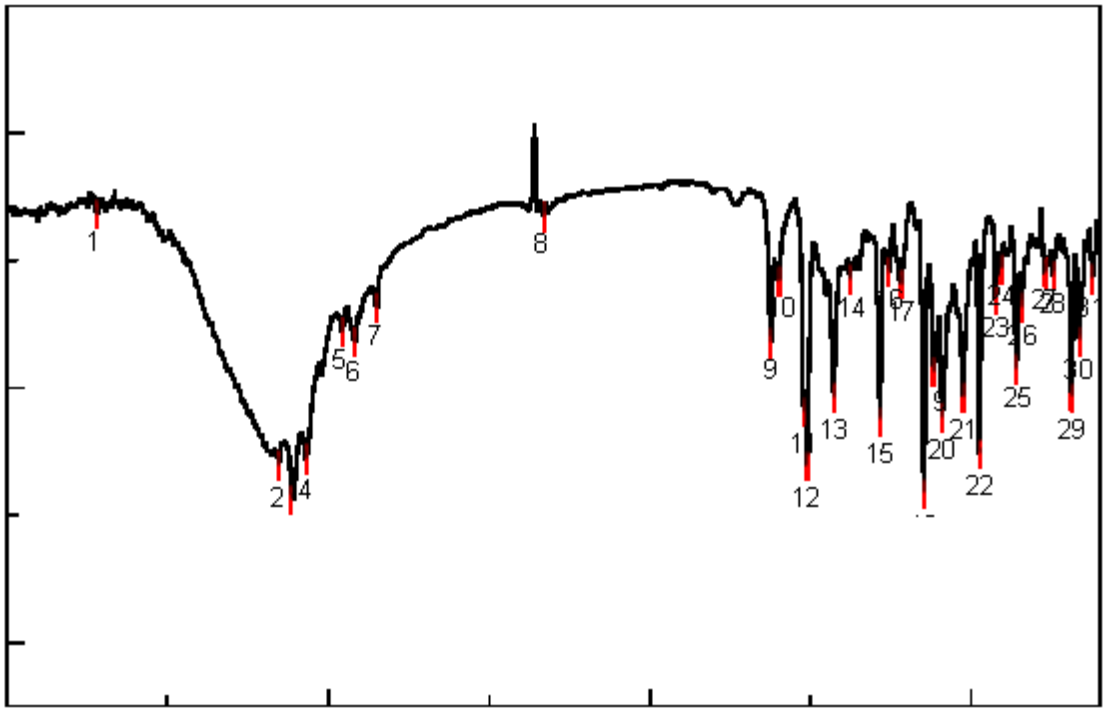


By Interpretation of FTIR peaks with their characteristics functional groups, it was observed that there was no interactions between drug and excipients for the formulations since there was no much deviation in peaks obtained for formulations (MH4,CH4,CE4,HE4) when compared with the Fluconazole drug standard.

4.Preformulation Studies:

controlled release layer blend showed angle of repose between 26.24^0 to 29.62^0,bulk density between 0.3892 gm/ml to 0.4426 gm/ml,tapped density between 0.3806 gm/ml to 0.4167 gm/ml ,hausner ratio between 1.05 to 1.15 ,compressibility index between 8.09 to 12.08,these results are presented in the table no12.

PRE-COMPRESSION EVALUATION:

Table-12:Pre-compression parameters of powder blend

Formulation code	Angle of repose (Degrees)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (%)	Hausner's ratio
MH1	28.32	0.4180	0.3842	8.09	1.1
MH2	26.24	0.4001	0.4024	8.92	1.1
MH3	28.14	0.4426	0.4140	9.02	1.08
MH4	26.31	0.4000	0.3922	7.09	1.1
CH1	28.42	0.4202	0.4021	5.28	1.15
CH2	29.22	0.4062	0.4426	12.04	1.1
CH3	29.62	0.3930	0.3968	11.06	1.1
CH4	27.68	0.4195	0.3806	5.14	1.12
CE1	28.52	0.4195	0.4165	4.78	1.12
CE2	28.62	0.4126	0.3824	9.06	1.14
CE3	29.39	0.3996	0.3964	12.08	1.15
CE4	27.94	0.3982	0.3825	10.02	1.15
HE1	27.54	0.4062	0.4028	9.09	1.05
HE2	28.96	0.3892	0.3872	4.07	1.14
HE3	28.81	0.4324	0.4320	6.28	1.14
HE4	27.68	0.4124	0.4108	8.65	1.1

5. POST-COMPRESSION EVALUATION OF TABLETS:

Evaluation of physical parameters:

Table-13:Physical parameters of prepared tablets

Formulation code	Weight variation (mg), n=20	Hardness (Kg/cm^2), n=5	Thickness (mm), n=3	Friability (%)	Assay (%Drug content), n=3
MH1	0.94	5.1	3.2	0.52	91.32
MH2	0.98	4.9	3.1	0.46	93.25
MH3	0.96	5.1	3.1	0.61	92.54
MH4	0.88	5.2	3.2	0.72	94.62
CH1	0.89	5.4	3.1	0.56	92.51
CH2	0.94	5.2	3.2	0.68	93.12
CH3	0.92	4.8	3.4	0.62	93.62
CH4	0.94	5.5	3.2	0.68	95.74
CE1	0.88	4.8	3.1	0.51	92.47
CE2	0.87	5.2	3.2	0.48	91.32
CE3	0.88	5.4	3.3	0.61	94.12
CE4	0.88	5.3	3.2	0.56	94.68
HE1	0.96	4.8	3.1	0.71	93.53
HE2	0.98	5.2	3.2	0.58	90.25
HE3	0.92	5.1	3.2	0.65	94.68
HE4	0.86	5.3	3.4	0.68	94.82

Physical properties of the tablet for all formulation were evaluated and data given in table no 12, Fromweight variation test it is observed that weight of all formulations varies between 0.87 to 0.98% , Hardness of the tablet was evaluated by using pfizer hardness tester ,result showed in the range of 4.8 to 5.4 kg/cm^2, thickness of the tablet were foundeinbetween 3.1mm to 3.4mm.Friability result gave percentage loss ranging from 0.46 % to 0.72 % for all the formulation which is with in prescribed limit (± 1%).

6.Invitro Drug Release Profile :

Table-14 : Results of *in-vitro* drug release study of Maltodextrin-HPMC

Time(hrs)	MH1	MH2	MH3	MH4
0	0	0	0	0
1	11.27	7.171	8.859	12.27
2	22.96	15.6	15.18	16.45
3	29.73	21.93	24.04	23.2
4	37.12	32.06	32.06	29.53
5	46.26	38.81	44.71	37.12
6	54.96	43.03	56.53	44.71
7	65.54	54.42	62.43	53.78
8	74.56	67.52	71.61	62.37

Fig.11:Dissolution Profiles of Formulations MH1-MH4

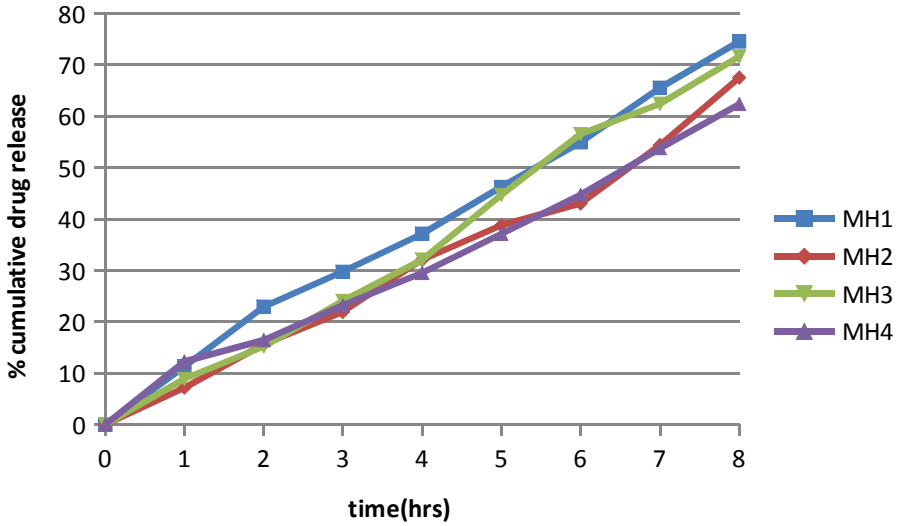


Table-15 : Results of *in-vitro* drug release study of Carbopol 940-HPMC

Time(hrs)	CH1	CH2	CH3	CH4
0	0	0	0	0
1	9.703	8.85	8.92	6.35
2	15.58	15.18	15.42	10.91
3	24.46	21.93	24.21	14.28
4	35.43	30.79	31.32	20.94
5	46.4	38.81	37.18	27.42
6	55.68	46.82	42.18	36.46
7	63.39	52.31	50.62	45.52
8	71.74	61.59	58.73	52.32

Fig.12:Dissolution Profiles of Formulations CH1-CH4

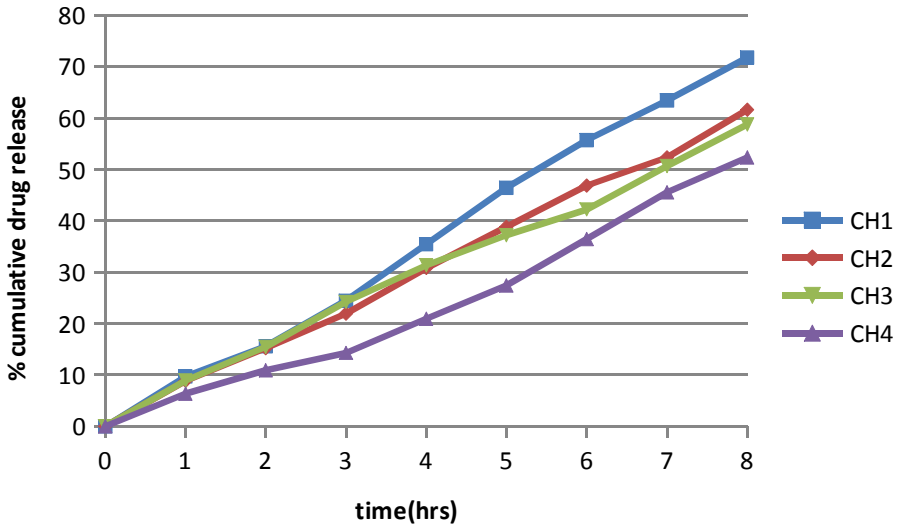


Table-16: Results of *in-vitro* drug release study of Carbopol 940-Ethyl Cellulose

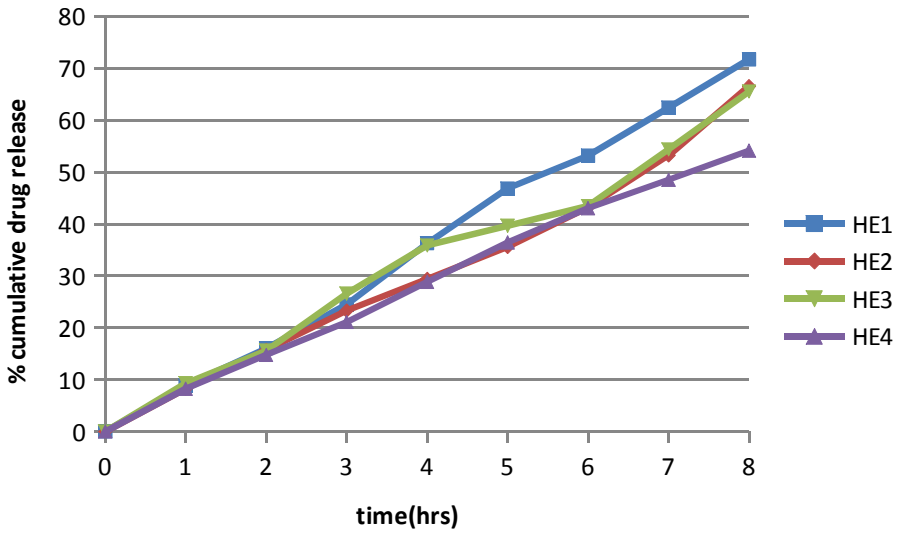
Time(hrs)	CE1	CE2	CE3	CE4

0	0	0	0	0
1	8.859	8.85	7.171	6.75
2	15.18	15.18	13.07	11.81
3	24.04	21.93	20.5	17.29
4	32.06	30.79	27.5	21.93
5	44.71	38.81	35.85	28.68
6	56.53	46.82	44.32	37.43
7	62.43	52.31	53.64	46.92
8	71.64	61.59	59.25	55.84

Fig.13:Dissolution Profiles of Formulations CE1-CE4

Table-17: Results of *in-vitro* drug release study of HPMC-Ethyl CelluloseXTime(hrs)	HE1	HE2	HE3	HE4
0	0	0	0	0
1	8.859	8.24	9.281	8.22
2	16.03	15.71	15.6	14.76
3	24.46	23.28	26.57	21.09
4	36.28	29.42	35.85	28.84
5	46.82	35.56	39.65	36.45
6	53.15	43.12	43.45	43.03
7	62.43	53.22	54.37	48.51
8	71.71	66.54	65.52	54.15

Fig.14 :Dissolution Profiles of Formulations HE1-HE4



After *invitro* dissolution studies from MH1-MH4,CH1-CH4,CE1-CE4,HE1-HE4 it was observed that formulation CH4 showed least release since the polymers carbopol 940,HPMC holds the drug effectively,CH4 was choosen as the best formulation for controlled release of drug.

7. ANTIMICROBIAL STUDIES

Fig.15 : Zone of Inhibition of Maltodextrin – HPMC(MH4)

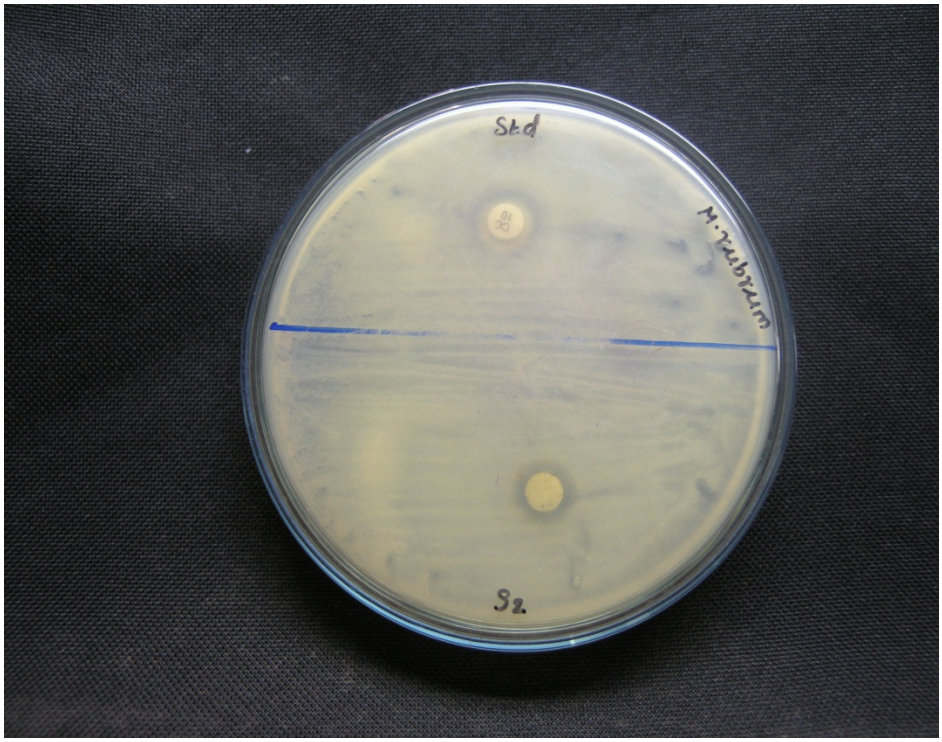


Fig.16 : Zone of Inhibition of Carbopol 940 – HPMC(CH4)

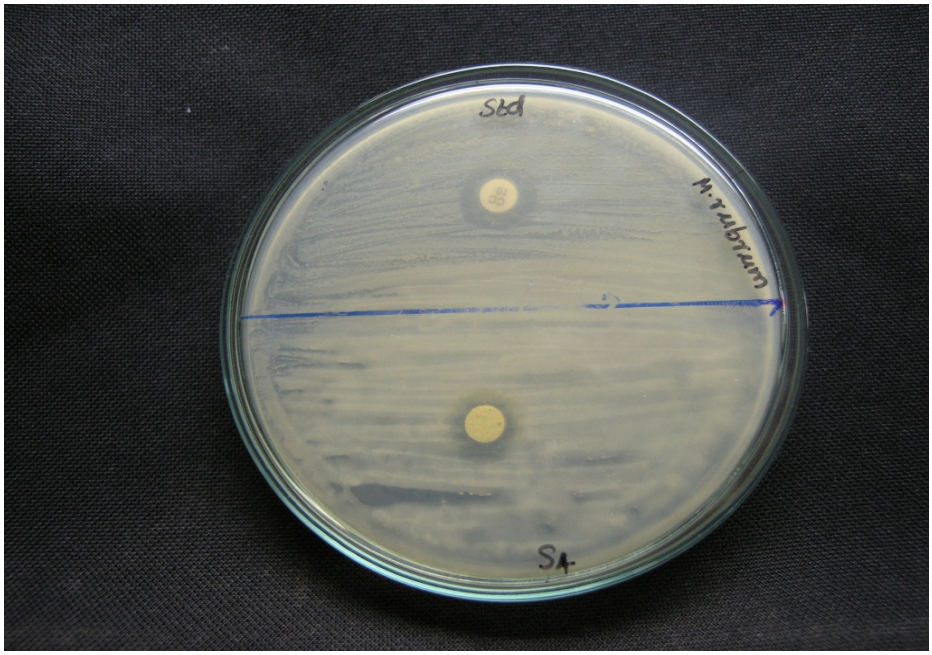


Fig.17 : Zone of Inhibition of Carbopol 940 -Ehyl Cellulose(CE4)

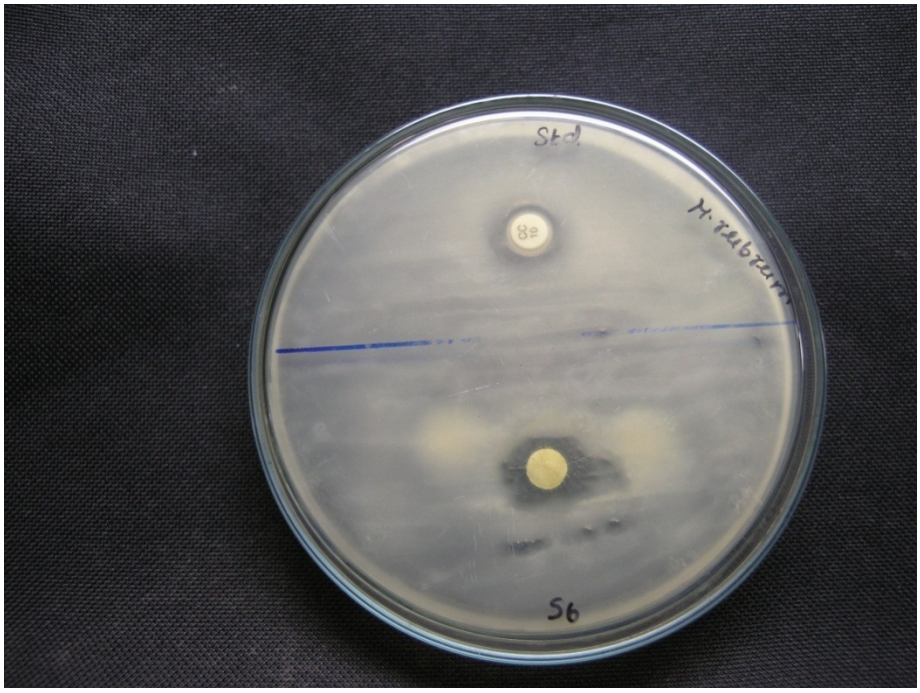
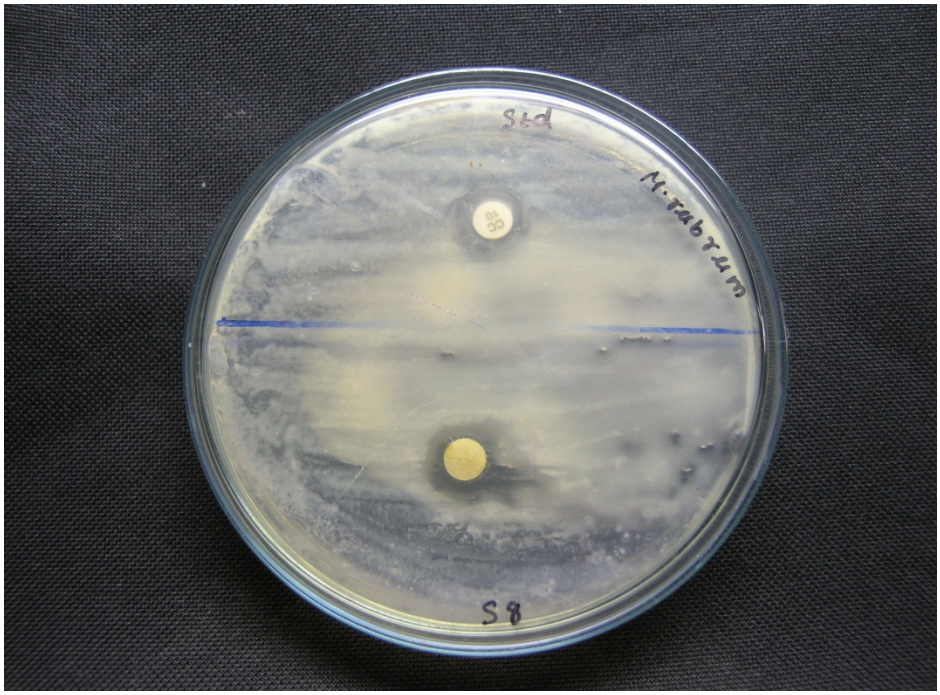


Fig.18 Zone of Inhibition of**:** HPMC - Ethyl Cellulose(HE4)



Results of Antimicrobial Study :

Table -18 : Zone of Inhibition of Formulations MH4,CH4,CE4,HE4

Formulation	Zone of inhibition(mm)
MH4	13
CH4	14
CE4	16
HE4	15

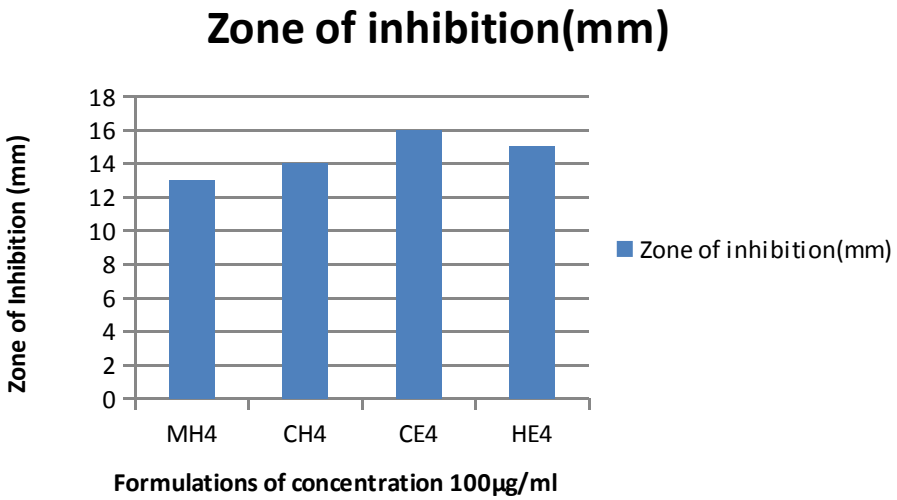


Fig.19 :Graph showing Zone of Inhibition of MH4,CH4,CE4,HE4

By antimicrobial studies it was observed that formulations MH4,CH4,CE4,HE4 showed zone of inhibition 13mm,14mm,16mm,15mm respectively indicating that these formulations are having antifungal activity.

8.Drug Release Kinetics

The *in vitro* drug release data were subjected to kinetic analysis by plotting various kinetic equations like zero order, first order, Higuchi, and Hixon crowells plot. They were also subjected for peppas plot in order to find out the mechanism of release from the prepared tablets . The kinetic analysis data of all the formulations were shown in Table no 19.

The kinetic model that best fits with the release data of formulation was evaluated by the correlation coiefficient (R^2) values. According to the values obtained it was found that all the formulations showed a higher linearity with zero order plots with R^2 values ranging from 0.954 to 0.997 indicating controlled release of drug from the prepared formulation . Formulation MH-4, CH-4, CE-4 and HE-4 gave a best fit for first order equation describing drug release rate with concentration of drug.

Mechanism of drug release:

Mechanism of drug release data can be assist by plotting the drug release data with Koresmeyer-peppas equation. The release exponent (n) value indicates the mechanism of drug transport from the matrix system. When the n value is equal to 0.5 indicates Fickian diffusion or anomalous, 0.45-0.89 indicates non-fickian transport more than 0.89 indicates Super case II transport.

The slope values obtained from the formulation ranged from 0.896 to 1.088 revealed the fact that drug release follows super case II transport diffussion posibly due to polymer chain errosion and swelling.

Table-19 :Results of drug release kinetics analysis

Formulations	zero-order	First-order	Higuchi	hixson-crowell	korsmeyer-peppas

R^2	R^2	R^2	R^2	R^2	n	R^2
MH1	0.954	0.962	0.956	0.987	0.974	0.986
MH2	0.995	0.953	0.96	0.985	0.952	0.994
MH3	0.991	0.946	0.978	0.979	0.898	0.995
MH4	0.992	0.982	0.987	0.958	0.932	0.998
CH1	0.934	0.861	0.986	0.905	0.896	0.985
CH2	0.98	0.874	0.992	0.927	0.971	0.992
CH3	0.997	0.927	0.978	0.968	1.005	0.998
CH4	0.991	0.972	0.978	0.977	1.022	0.995
CE1	0.997	0.942	0.974	0.975	0.949	0.995
CE2	0.996	0.942	0.969	0.978	1.024	0.995
CE3	0.983	0.953	0.952	0.984	1.063	0.99
CE4	0.984	0.962	0.957	0.979	1.088	0.978
HE1	0.992	0.949	0.962	0.98	1.025	0.989
HE2	0.983	0.953	0.952	0.984	1.063	0.99
HE3	0.985	0.957	0.951	0.979	0.961	0.976
HE4	0.996	0.964	0.977	0.965	1.032	0.995

9.Statistical Analysis :

DESIGN SUMMARY AND RESPONSES

Table 20 : Design summary and responses of Statistical Analysis

			Response			
Formulation	Factor-A	Factor-B	Hardness Kg/cm^2	Release at 1^{st}hr in %	T50% in hrs	Zone of inhibition in mm

MH4	-1	-1	5.4	12.27	7	12
CH4	1	1	5.5	6.35	8	14
CE4	-1	1	5.3	6.75	8	16
HE4	1	-1	5.3	8.25	8	15

RESULTS OF STATISTICAL ANALYSIS

Table 21 : ANOVA Response for Hardness

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	20.799	2	10.400	0.031	0.227
Within Groups	1.125	1	1.125		
Total	21.924	3			

Statistically significant at $\alpha < 0.05$

Table 22 : ANOVA Response for Release at 1st hour

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5.000	3	1.667	0.0025	
Within Groups	0.000	0			
Total	5.000	3			

Statistically significant at $\alpha < 0.05$

Table 23 : ANOVA Response for T50% in hours

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	0.750	3	0.250	0.0036	
Within Groups	0.000	0			
Total	0.750	3			

Statistically significant at $\alpha < 0.05$

Table 24 : ANOVA Response for Zone of Inhibition

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	0.028	3	0.009	0.225	
Within Groups	0.000	0			
Total	0.028	3			

Statistically significant at $\alpha < 0.05$

Table 25 : comparison chart of predicted and actual values for optimized Formulation

Formulations	**Hardness**		**Release at 1 hr**		**T50% in hr**		**Zone of inhibition in mm**	
Optimized formulation	Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted
	5.37	5.5	8.40	8.5	7.75	8.0	14.25	15.0

Effect of formulation variables on hardness of the tablet

In this case hardness of the tablet was found to be significant with an F value 0.031, indicating adequate fitting of the 2^2 factorial model. Both factors A,B were found to be significantly effective on the hardness of the tablet.

Effect of formulation variables on release at 1st hour

The Fluconazole release at 1st hr was found to be significant with a F value of 0.0025, indicates adequate fitting to 2^2 factorial model. Both factors A,B were found to be significantly effective on the release of a tablet at 1st hour.

Effect of formulation variables on time required for T50% of drug release.

The T50% was found to be highly significant with an F value of 0.0036 indicating the adequate fitting of the 2^2 factorial model. Both factors A,B were found to be significantly effective on the time required for T50% of drug release**.**

Effect of formulation variables on zone of inhibition

The zone of inhibition was found to be not significant with the F value of 0.225, indicating inadequate fitting of the 2^2 factorial model. Both factors A,B were found to be not significant indicating that both polymers does not have any effect on zone of inhibition.

comparison of predicted and actual values for optimized Formulation

By comparing predicted and actual values it was observed that optimized formulation(CH4) was choosen as the best formulation since it showed least deviation from that of predicted values.

SUMMARY

The present study was aimed at preparing a tablet containing fluconazole for controlled release of drug. Frequent administration can be avoided by administering controlled release drug delivery system.It may improve efficiency in treatment with reduction in total dose total dose and also avoid dose dumping. By using Maltodextrin,HPMC,carbopol 940,Ethyl cellulose the release retardant was observed and 2^2 factorial design was made,16 formulations were prepared.All the formulation showed good correlation with pharmacopoeial standard for tablet, *invitro* dissolution data showed controlled release pattern for all the formulations.Formulations were optimized statistically and results showed that MH4,CH4,CE4,HE4 close value to the optimized parameters and CH4 was choosen as the optimized formulation, since it showed least deviation from the predicted response.

CONCLUSION

The controlled drug delivery is a promising approach to achieve *in vitro* release of drug by using polymers like Maltodextrin,HPMC,Carbopol-940,Ethylcelluose.Combination of Carbopol 940 and HPMC had resulted in controlled drug release. A systematic study using a 2^2 factorial design revealed that by selecting a suitable composition of carbopol 940 and HPMC(CH4), the desired dissolution profile could be achieved. The optimized formulation gave best result in drug release was in accordance with the USP dissolution criteria for controlled release tablet for Fluconazole. prepared formulations were showing zero-order release pattern.It could be used as once a day formulation. This can also reduce the over dose effects such as hallucinations and paranoid behaviour. However, appropriate balancing between various levels of the 2 polymers could be an imperative to acquire proper controlled release. High degree of prognosis obtained using SPSS stastistics corroborates that it is quite efficient in optimizing drug delivery systems that exhibit non-linearity in response.

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